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George A. Moulton, president of the National Association Boards of Pharmacy, was born in Lewiston, Me., son of George A. and Anna A. (née Frieze) Moulton.

His early education was received in the grade schools of Lewiston and the high school of Palmer, Mass. He entered Central Maine Hospital for medical training, later changing to Lawrence General Hospital and then he matriculated at Massachusetts College of Pharmacy. He received the degree of P.D. and later, Ph.C. He served as president of his class and edited a "Syllabus on Materia Medica," published by his class. Prior to graduation he was employed with Irving P. Gammon and Lyman W. Griffin, and on graduation, engaged with Nelson S. Whitman of Nashua, N. H. He bought the pharmacy he now operates in Peterborough, N. H., in 1917.

He joined the State Association and the AMERICAN PHARMACEUTICAL ASSOCIATION in 1915. He prepared and put into operation the "New Hampshire Plan." He edits the Association bulletins, the "President's Letters" and is Commissioner of Pharmacy of New Hampshire. President Moulton served as vice-president for two terms of District No. 1, N. A. B. P., he was secretary of the Section on Education and Legislation, A. PH. A., in 1936 and vice-chairman in 1937. He is a member of the N. A. R. D. and has served on important committees. He is a former president of the Rotary Club, member of Unitarian Laymens League and Parent Teacher Organization. Mr. and Mrs. Moulton have two sons—one a sophomore in high school, and the other a student in Massachusetts College of Pharmacy.

EDITORIAL

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STANDARD DIGITALIS POWDER OF U. S. PHARMACOPŒIA XI.

THE detailed report of the studies on Digitalis Powder by Edmunds, Moyer and Shaw (JOUR. A. PH. A., April 1937, pages 290–305) again emphasizes the necessity for a uniform reference standard for this bioassay. All bioassays are comparative; the variability of animals is becoming more appreciated as better methods of standardization are developed. A satisfactory bioassay requires the duplication of intensity of effect following administration of a *standard* and of an *unknown* sample under essentially identical conditions. The older concept of uniformity in animals, reflected by the adoption of certain numerical values which should produce described effects, is disappearing. It is now recognized that more accurate results are obtainable when simultaneous tests are made on the unknown and the reference standard, and potency evaluated in terms of such standard.

The analytical results show how indefinite the term "cat unit" may be, even when the same laboratory is comparing several samples under presumably identical conditions. Variations in technique, such as the use of a different anesthetic, or a different period for the production of death, or even differences in interpretation of death itself, may produce marked differences in the quantity of digitalis considered to be "one cat unit." These differences are so great as to be potentially dangerous, when considered for any animal unit.

When tests were conducted by the U. S. P. XI one-hour frog method, the U. S. P. Reference Powder was found to be 134% of the potency of the International Standard Reference Digitalis Powder; the British 1928 standard 119% and the Canadian 1928 standard 116%. When tested by the "Four-Hour Frog Method," the "Twelve-Hour Frog (Limitless) Method," and the author's modification of the cat method, different ratios were obtained showing the impracticability of developing factors for the conversion of results upon one animal into results by any other animal method.

By close attention to analytical procedures tests by various frog methods, using different amounts of digitalis, different lots of frogs, and working at different times of the year, showed a maximum variation of 8%, which is well within the limits of error allowable for bioassays conducted within the same laboratory. When different laboratories test the same sample, additional variations in technique may be expected to produce greater variations.

Among the other independent studies being made, in connection with Digitalis, there are two for which the results of these investigations will be useful: *First*, what is the ratio of potency required for U. S. P. X Tincture of Digitalis, as compared with U. S. P. XI Tincture of Digitalis; *second*, which method of bioassay will give results most closely in agreement with clinical value for digitalis and its preparations? The report by Edmunds and associates will be an assistance in connection with these studies, so long as its principal thesis is observed: tests must be conducted under rigidly prescribed technique and using U. S. P. Standard Digitalis Powder as the basis for these conclusions.—JAMES C. MUNCH.

COMMENCEMENTS ARE PERIODS OF PERLUSTRATION.

THIS writer expressed the following thought on another occasion: Alumni represent assets or liabilities to the institutions which prepared them for their life work and the profession of which they are part—these annual events are periods of perlustration.

In his Dallas address, former President Robert C. Wilson of the American Association of Colleges of Pharmacy brought out points setting a standard of measurement for professional schools. These thoughts which were discussed by him and shaped into a comprehensive study are given very incompletely in this comment, in titular words or phrases: A professional school should assume leadership in its respective field; it should acquaint itself with conditions and practices and trends in that respective field; it should concern itself with the personal character of its graduates; it should identify itself with all proper agencies within the profession. Service should have as a motive ideals above personal gain; it should influence constructive changes for improvement.

The following concluding paragraphs are quoted from the address of President Harmon W. Caldwell, of the University of Georgia, on the same occasion: "The educated man must strive always to see things in their true perspective. He must not forget that all phases of the world's work may be, in the final analysis, equally important. The common, ultimate goal of all is the building of a finer civilization, a civilization in which the reasonable needs of all may be provided for, and in which each individual may find for himself a measure of happiness and contentment.

"Professional men are peculiarly responsible for their particular part of the work that must be done to create this better civilization. They must do that well, but they must also coöperate with workers in other fields so that, through the united efforts of all, we as a people may come to the attainment of our common aspirations."

THE VENEREAL CONTROL.

SURGEON GENERAL PARRAN has started effective work for the control of venereal diseases, but there are always possibilities of improving plans. It is a campaign in which every one can help; no single group can bring about all the necessary results. The details of Public Health services for securing results extend to some professional and social activities that have rather indirect connection, but all phases should be studied.

Only in recent years has early education been thought of in connection with moral questions; secrecy has been deemed the best means for protecting youth from the dangers infection may bring to them. There are immoral persons who lead the youth to satisfy curiosity by supplying the means and others, if unfortunate results obtain, who will acquaint the victim with the means of self-treatment (?). Here the dangers multiply and how best to deal with the problems, becomes very difficult. Coöperation can only result when the conditions are considered; accusation and placing charges of the responsibility on one group are not the means for accomplishment. The unfortunate must be made to realize that they may have help without undue publicity and they must do their part; they must be made to understand that early in the history of their cases it is important to receive proper advice and treatment.

A recent investigation brought out information that might have been surmised but, nevertheless, surprising. The experiences gathered by some hardly ever protect others and every one of these experiences is paid for most dearly. Undoubtedly conditions are different and it may be a source of satisfaction to believe that they are in general no worse than a century or more ago. Improved moral values and higher standards of ethics should obtain.

SCIENTIFIC SECTION

BOARD OF REVIEW OF PAPERS.—*Chairman*, F. E. Bibbins; H. M. Burlage, W. G. Crockett, E. V. Lynn, C. O. Lee, L. W. Rising, L. W. Rowe, Heber W. Youngken, F. V. Lofgren, J. C. Krantz, Jr.

A STUDY OF SEVERAL SPECIES OF THE GENUS MONARDA.*[1]

BY B. V. CHRISTENSEN[2] AND R. S. JUSTICE.[3]

SECTION NO. 3—SUMMARY OF ASH ANALYSES.

In recent years investigation of the ash constituents of the Monardas has brought into literature chemical analyses on several species. In the present study three species, *Monarda pectinata*, *Monarda menthæfolia* and *Monarda punctata* **var.** *leucantha* were examined. In the following tabulations the analyses presented by A. A. Harwood on *Monarda punctata* (1) and *Monarda fistulosa* (2) are also used. The results are calculated to the basis of anhydrous plant material in order to obviate any discrepancies due to variations in the moisture contents of the samples. The soil samples presented are those of typical soils frequented by the Monardas in the states of Wyoming (3), Wisconsin (4) and Florida where the various plant samples were collected.

After a careful perusal and checking of results no outstanding anomalies can be definitely pointed out except in two instances.

In the case of the sulfate determinations in Table I below, it is interesting to note that there is a marked variation in the content of the flower heads and leaves of *Monarda fistulosa* as compared with the other species. This variation is apparently not due to the soil or circumstances other than the fact that the plant itself must enter into the special selectivity for the ion. With regards to this marked variation, the writer calls attention to the fact that *Monarda fistulosa* is the only Monarda studied to date in which the presence of thymol has not been definitely established.

TABLE I.—SULFATE IN THE ASH, PERCENTAGE RESULTS.

Plant.	Flower Heads or Bracts.	Leaves.	Stems.	Roots.	Soil.
Monarda menthæfolia	0.31	0.27	0.08	0.12	0.07
Monarda fistulosa	0.54	0.71	0.17	0.15	0.074
Monarda punctata	0.36	0.28	0.32	0.15	0.074
Monarda punctata **var.** *leucantha*	0.40	0.25	0.27	0.11	...
Monarda pectinata	0.26	0.24	0.09	0.10	0.07

Note that the leaves of the thymol producing plants have a sulfate content of from 0.24 to 0.28 per cent. *Monarda fistulosa* leaves contain 0.71 per cent or approximately double the amount.

The next important and obvious variation seems to be in the calcium contents of the leaves and flower heads. See Table II. The variations are apparently not

* Scientific Section, A. PH. A., Dallas meeting, 1936.

[1] From a dissertation presented in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Florida, August 1935.

[2] Director of the School of Pharmacy, University of Florida.

[3] Graduate Assistant in Pharmacognosy, University of Florida, 1933–1935.

due to the variations of calcium in the soil but rather to the plant itself or its environment. The writer again calls particular attention to the fact that *Monarda fistulosa*, the carvacrol producing plant, has distinctively the lowest calcium content. *Monarda menthæfolia*, the plant closest related to *Monarda fistulosa* morphologically and the plant producing less thymol and more carvacrol than the other thymol containing plants, comes next to the *fistulosa* in calcium content. All the thymol producing plants contain more than one per cent of calcium in their leaves.

TABLE II.—CALCIUM IN THE ASH, PERCENTAGE RESULTS.

Plant.	Flower Heads or Bracts.	Leaves.	Stems.	Roots.	Soil.
Monarda menthæfolia	0.82	1.11	0.34	0.55	0.82
Monarda fistulosa	0.63	0.77	0.20	0.35	1.14
Monarda punctata	0.78	1.26	0.49	0.26	1.14
Monarda punctata **var.** *leucantha*	2.32	2.19	0.62	0.37	Above average
Monarda pectinata	2.00	2.82	1.10	0.50	0.82 to 1.47

The remaining analyses showed no marked variations. This is the case of the magnesium determinations given in Table III.

TABLE III.—MAGNESIUM IN THE ASH, PERCENTAGE RESULTS.

Plant.	Flower Heads or Bracts.	Leaves.	Stems.	Roots.	Soil.
Monarda menthæfolia	0.15	0.31	0.10	0.019	0.75
Monarda fistulosa	0.12	0.13	0.018	0.074	0.073
Monarda punctata	0.10	0.18	0.029	0.02	0.073
Monarda punctata **var.** *leucantha*	0.35	0.38	0.095	0.104	0.76
Monarda pectinata	0.23	0.28	0.13	0.13	0.75

The quantity of magnesium present seems to be dependent upon the selectivity of the plant and to its chlorophyll content, certainly not on the soil content of the element.

TABLE IV.—IRON IN THE ASH, PERCENTAGE RESULTS.

Plant.	Flower Heads or Bracts.	Leaves.	Stems.	Roots.	Soil.
Monarda menthæfolia	0.27	0.50	0.13	0.54	2.84
Monarda fistulosa	0.11	0.095	0.050	0.19	2.365
Monarda punctata	0.10	0.15	0.09	0.048	2.365
Monarda punctata **var.** *leucantha*	0.018	0.02	Trace	0.010	0.1 to 0.5
Monarda pectinata	0.16	0.28	0.05	0.56	2.84

The iron content of the Monardas seems to be influenced by the amount of iron in the soil. Aluminum is not influenced by the quantity in the soil. See Table V below:

TABLE V.—ALUMINUM IN THE ASH, PERCENTAGE RESULTS.

Plant.	Flower Heads or Bracts.	Leaves.	Stems.	Roots.	Soil.
Monarda menthæfolia	1.02	0.66	0.55	0.38	4.50
Monarda fistulosa	0.15	0.18	0.049	0.20	8.197
Monarda punctata	0.25	0.25	0.12	0.07	8.197
Monarda punctata **var.** *leucantha*	0.13	0.075	0.027	0.062	...
Monarda pectinata	0.70	0.99	0.21	0.50	4.50

The foregoing correlation of data is the initial step in an attempt to find, if possible, the reason for the peculiar variation in constituents, especially the phenolic constituents, in the

Monardas. It may or may not be due to the presence or absence of elements or radicals in various species. At the same time, this correlation of data may, in time, point out species differences.

In the absence of similar data from other species it is impossible to carry this study further at the present time. However, other determinations were made in the course of the present investigation and the results are presented herewith in Tables VI, VII and VIII.

TABLE VI.—MONARDA PUNCTATA VAR. LEUCANTHA, PERCENTAGE RESULTS.

Determination.	Flower Heads Early.	Leaves.	Stems.	Roots.	Flower Heads Late.
Silicate (SiO_3)	0.27	0.74	0.44	51.99	0.52
Phosphate (PO_4)	0.91	0.71	0.48	0.47	1.14
Alkalinity of Ash (CO_3)	5.68	5.65	1.48	1.31	5.72

TABLE VII.—MONARDA MENTHÆFOLIA, PERCENTAGE RESULTS.

Determination.	Flower Heads.	Leaves.	Stems.	Roots.
Chlorine (Cl)	0.016	0.049	0.044	0.025
Silicate (SiO_3)	4.45	2.59	0.58	9.38
Phosphate (PO_4)	0.29	0.31	0.21	Trace
Alkalinity of Ash (CO_3)	3.27	3.10	2.44	1.93

TABLE VIII.—MONARDA PECTINATA, PERCENTAGE RESULTS.

Determination.	Flower Heads.	Leaves.	Stems.	Roots.
Chlorine (Cl)	0.028	0.026	0.033	0.021
Silicate (SiO_3)	3.59	12.21	1.17	2.60
Phosphate (PO_4)	0.11	Trace	0.086	Trace
Alkalinity of Ash (CO_3)	2.52	1.97	1.82	1.94

Method Used.—The results above are all calculated on the basis of anhydrous plant material.

The various elements and radicals were determined as follows:

Sulfate (SO_3) as barium sulfate (5).
Calcium (Ca) as the oxalate and weighed as the sulfate (6) or oxide (7).
Magnesium (Mg) as the pyrophosphate (8).
Iron (Fe) by permanganate titration (9).
Aluminum (Al) by difference (10).
Silicon dioxide (SiO_3) as such (11).
Phosphate (PO_4) as the ammonium phosphomolybdate (12) by titration.
Carbonate (CO_3) as alkalinity of ash by titration (13).
Chlorine (Cl) by titration (14).

CONCLUSION.

The more common elements and radicals in *Monarda punctata* **var.** *leucantha*, Nash., *Monarda menthæfolia*, Benth. and *Monarda pectinata*, Nutt., were determined. In some cases these values were compared with similar results for *Monarda punctata*, L., and *Monarda fistulosa*, L. Calcium and Sulfate determinations indicate possibilities of a correlation between ash analyses and the occurrence of characteristic phenolic constituents.

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(7) Treadwell and Hall, *Analytical Chemistry*, 2, 86 (1928).
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(9) A. O. A. C. Methods, 41 (1920).
(10) *Ibid.*, 41.
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(14) A. O. A. C. Methods, 43 (1920).

A STUDY OF SEVERAL SPECIES OF THE GENUS MONARDA.*[1]

BY B. V. CHRISTENSEN[2] AND R. S. JUSTICE.[3]

SECTION NO. 4—THE HISTOLOGY OF MONARDA MENTHÆFOLIA VAR. LEUCANTHA.

Since there have been questions arising as to the authenticity of classifying some groups of Monardas as independent species, the histology of the various Monarda species is becoming important. As a means of increasing the number of studies on Monardas now available the histology of *Monarda punctata* **var.** *leucantha*, Nash., is presented in the following paper.

Monarda punctata **var.** *leucantha* shows the characteristics of the Genus Monarda of the Labiatæ (Lamiaceæ) Family as follows:

Corolla two-lipped with lower lip three-lobed and middle lobe longer than lateral ones, two stamens, filaments elongate and anthers with divergent sacs, gynœcium with two carpels, a four-celled ovary, a fruit with four nutlets included in the calyx, leaf blades toothed, flowers in dense racemes, calyx elongated with five lobes. It is also assigned to subgenus Cheilyctis due to the fact that the flower clusters are mainly axillary, borne in spike-like interrupted panicles and the stamens do not exceed the curved upper corolla lip. This variety differs from *Monarda punctata*, Linn., externally inasmuch as the corolla is white with purple spots while *Monarda punctata* corolla is yellow with purple spots. See Plates 1, 2, 2A and 3.

The following microscopical studies were carried out upon specimens which had been fixed in formol-acetic acid fixative and double stained with safranin and methylene blue.

THE HISTOLOGY AND DEVELOPMENT OF THE FLOWER.

In the sectioning of the flower heads the various stages in the development of the flower were obtained in detail. The first flower part to become differentiated from embryonic tissue was the calyx. Next the carolla develops and in the course of this development the filament and rudimentary anthers appear. The differentiation of the gynœcium begins at approximately the same time. Up to this time the tissue present is meristematic with no apparent differentiation into cells with other functions.

From this point the embryonic flowers develop the differentiated tissues such as parenchyma, vessels in the veins, epidermis, trichomes and glandular hairs, pollen and meristematic

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[1] A dissertation presented to the Graduate Council of the University of Florida in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Director of the School of Pharmacy, University of Florida.

[3] Graduate Assistant in Pharmacognosy, University of Florida, 1933–1935.

tissue or regenerative tissue of the ovary. Histologically the flower cluster shows the usual typical flower structures in the flowers of the raceme and also in the bract.

The bract externally is composed of epidermal cells and numerous one- to three- or four-celled simple, multicellular, non-branching, non-glandular hairs and scattered sessile, multicellular, glandular hairs. These hairs are typical of all epidermal coverings of *Monarda punctata*, **var.** *leucantha* and so, for simplicity, they will hereafter be referred to as glandular and non-glandular hairs. Internally the principal tissue of the bract is mesophyll. No palisade is present. There are also scattered bundles composed of vessels and fibers.

Plate No. 1.—Pen Drawing of the Flower of *Monarda punctata* **var.** *leucantha*, Nash. (× 5).

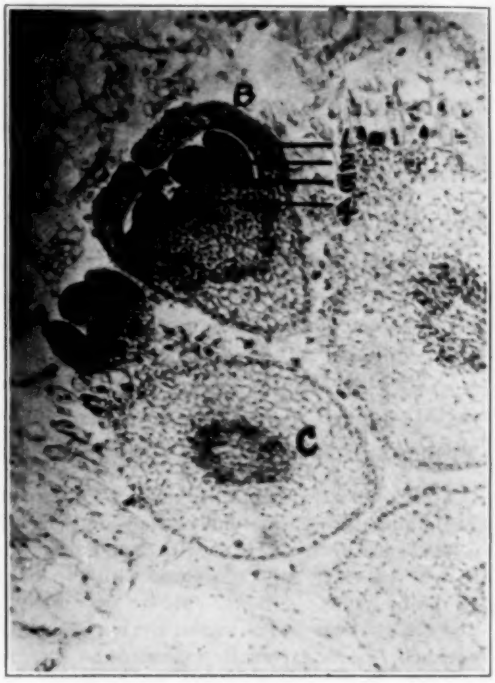

Plate No. 2.—Longitudinal Sections of Rudimentary Flower Buds (× 140). *A*—Bud showing differentiation of the calyx. *B*—Bud showing more advanced differentiation into the following: 1—the calyx; 2—the corolla; 3—the anthers; and 4—the pistil. *C*—The cross section of the receptacle of a florette.

The following parts of the flower are present:

(*a*) The calyx
(*b*) The corolla
(*c*) The stamens
(*d*) The pistil.

The calyx is composed of a simple epidermis on the internal surface while the external surface has glandular and non-glandular hairs in addition. Internally the tissues are parenchyma,

mesophyll and fibrovascular bundles. In all the specimens examined there were thirteen fibrovascular bundles present which coincided with the ribs of the calyx.

The corolla (Plates Nos. 3 and 4) is composed of epidermis, mesophyll, parenchyma and scattered vascular bundles. The inner wall of the corolla tube is composed of characteristically wavy-walled epidermis. There are also non-glandular hairs present in mature corollas.

The stamens, of which there are two, are composed of a two-lobed anther and a filament which is adnate to the corolla near its base. The anther is composed of two distinct lobes (Plate 3) which are united to the filament at their point of attachment and which are filled with pollen.

Plate No. 2A.—Longitudinal Sections of Rudimentary Flower Buds (× 140). *A*—A very rudimentary flower bud showing very little differentiation of tissues. Calyx not yet formed although it is beginning to differentiate. *B*—Differentiation has begun with the formation of the calyx. 1—is the calyx.

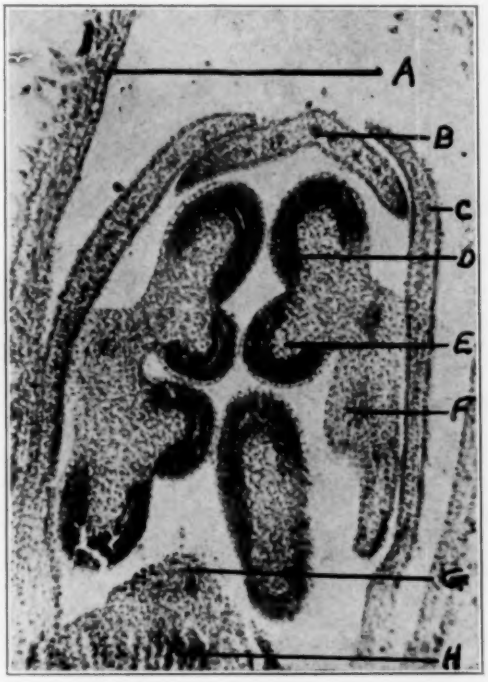

Plate No. 3.—Longitudinal Section of a Flower Bud (× 140). The bud has advanced from the rudimentary stage and is now approaching the stage at which it will flower. It shows the following: *A*—the calyx; *B*—the lip of the corolla; *C*—the corolla proper; *D*—the pollen developing in the anther, nucleus present; *E*—a lobe of the anther; *F*—the filament; *G*—the pistil; and *H*—the ovary.

The filaments are composed principally of parenchyma tissue and epidermis and a central cylinder of vascular tissue which traverses the length of the structure.

The pistil is composed of two carpels as indicated by the forking of the style (Plate 1) and by the median line which was found in numerous sections of the ovary in the progress of this study. Each carpel gives rise to two lobes which in turn develop into the four nutlets that compose the fruit of the plant. See Plate No. 4. Histologically the pistil is composed of parenchyma, ducts and meristematic tissue. The latter is found in the lobes of the ovary.

HISTOLOGY OF THE LEAF.

The petiole of the leaf of *Monarda punctata* **var.** *leucantha* is composed of a large double central fibrovascular bundle which is divided into a left and right half by a row of parenchyma cells. These bundles are composed of xylem strands surrounded by two to three rows of phloem.

The bundles themselves are surrounded by large thin-walled epidermis of the petiole. Laterally as the petiole approaches the leaf blade the petiole may also be composed of leaf blade tissues, *i. e.*, palisade and mesophyll. The epidermis is composed of typical epidermal cells and glandular and non-glandular hairs.

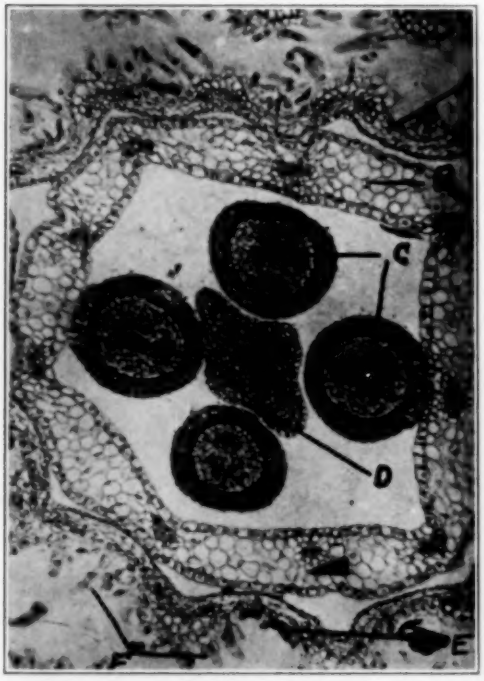

Plate No. 4.—Cross Section of the Flower (× 140). This section was taken at the level of the top of the lobes of the ovary. The following structures are seen. *A*—the calyx; *B*—the corolla; *C*—the lobes of the ovary; *D*—the pistil; *E*—very young glandular hairs showing the individual cells with nuclei; and *F*—very young epidermal hairs with nucleated cells.

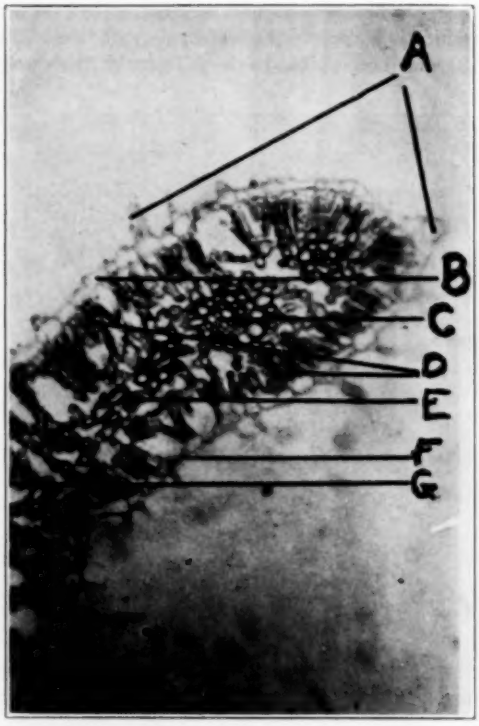

Plate No. 5.—Cross Section of the Lateral Edge of a Leaf (× 140). This section shows the following structures; *A*—the epidermal hairs; *B*—the epidermis; *C*—a vein; *D*—the upper and lower palisades; *E*—the mesophyll; *F*—the stoma; and *G*—a glandular hair.

The leaf blade consists of the midrib which is merely an elongation of the petiole and resembles it closely, the epidermis, palisade, parenchyma and conducting tissues. In cross section, the leaf internally is composed of a distinct upper palisade and in most cases a distinct lower palisade. See Plate No. 5. In less mature leaves the lower palisade is sometimes loosely arranged and resembles the mesophyll. Between the palisade layers there are two to three rows of mesophyll.

HISTOLOGY OF THE STEM.

The stem is composed of the following regions:

1. Epidermis
2. Cortex
3. Phloem
4. Cambium
5. Xylem
6. Pith (see Plate No. 6).

Externally the stem is composed of epidermis with slightly thickened and somewhat cutinized external cell walls. There are also to be found, scattered non-glandular hairs.

Under the epidermis in the corners there are bundles of non-lignified cells whose cell walls are composed of cellulose. The corners of these cells are characteristically thickened. This tissue is the collenchyma which is the characteristic strengthening tissue found in the corners of mint stems.

The remainder of the cortex is composed of six to eight rows of tangentially elongated parenchyma cells whose walls are perceptibly thickened.

In the phloem region there are four to eight rows of cells which are not well defined since they are small and thin walled. The phloem does contain well-defined and scattered sclerenchyma fibers which contain crystals.

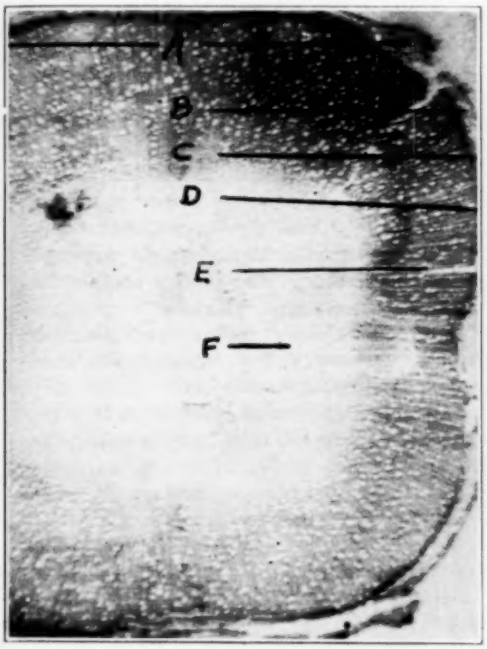

Plate No. 6.—Cross Section of the Stem (× 18). The cross section of the stem shows the following structures: *A*—the collenchyma; *B*—the cortex; *C*—the phloem; *D*—the cambium ring; *E*—the xylem; and *F*—the pith.

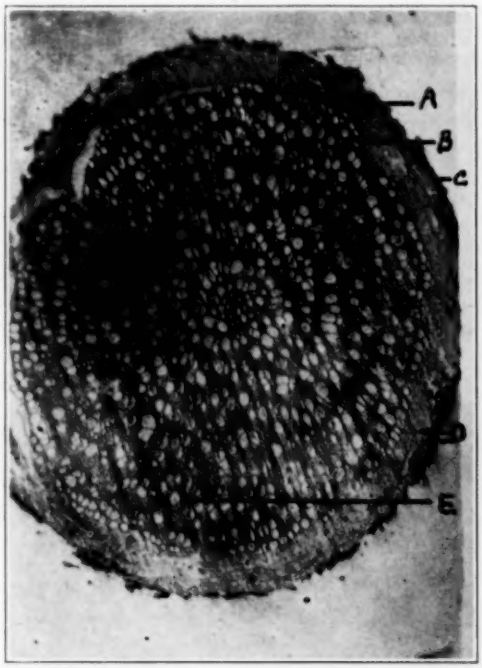

Plate No. 7.—Cross Section of the Root (× 25). The section shows the following structures: *A*—the phloem; *B*—the cambium ring; *C*—the cork; *D*—the cortical parenchyma of the cortex; and *E*—the xylem.

A well-defined cambium does not exist although there is a distinct line made up of compact cells which cannot be distinguished individually and which separates the phloem from the xylem.

Inside the cambium is a complete cylinder of woody tissue, highly lignified, which is composed of vessels and radially arranged fibers. The scattered vessels can be distinguished in cross section as the large isodiametric cells as compared to the small quadrangular and polygonal cells which are fibers and which are in radial rows.

The pith is located within the xylem ring and is composed of large isodiametric parenchyma cells except for a region adjacent to the xylem where the parenchyma cells are smaller and somewhat polygonal.

The longitudinal section shows the epidermis as somewhat longitudinally elongated cells. The cortical parenchyma is made up of quadrangular and longitudinally elongated cells. The phloem and xylem are difficult to distinguish but the sclerenchyma fibers are scattered through the phloem region and the crystals contained are easily detected. The xylem is composed of

pitted tracheal tubes and tracheids and the fibers are longitudinally arranged. The pitch parenchyma is made up of quadrangular cells which are arranged in longitudinal rows.

HISTOLOGY OF THE ROOT.

The root is composed of the following regions:

1. Cork
2. Cortex
3. Phloem
4. Cambium
5. Xylem (see Plate No. 7).

The cork is composed of a layer of four to nine rows of irregularly arranged cells which range in shape from tangentially elongated quadrangular cells to cells which are almost isodiametric. The outer layers of cells are compact and are often torn away and show lenticels.

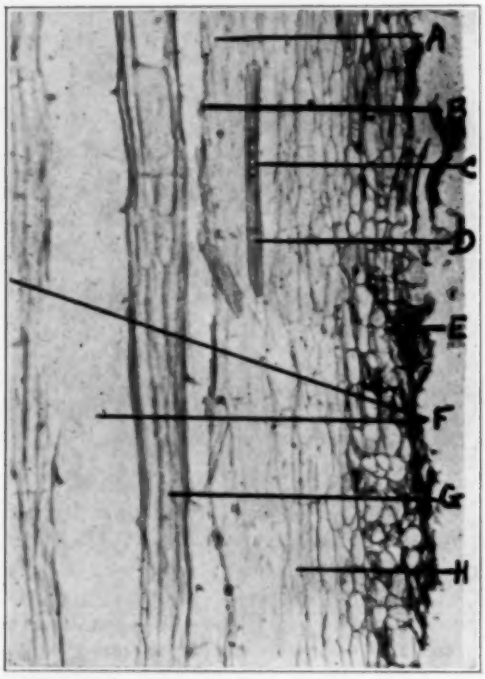

Plate No. 8.—Longitudinal Section of the Root (× 140). This section shows the following structures: *A*—the phloem; *B*—the cambium zone; *C*—crystals in the sclerenchyma fiber; *D*—crystal bearing sclerenchyma fiber; *E*—the cork; *F*—the ducts in the xylem; *G*—wood fibers; and *H*—the cortical parenchyma.

The cortex which lies directly under the cork is composed of approximately 15 rows of cells. There is apparently no differentiation between phloem and cortex in the root. The body of the cortex tissues is made up of thin-walled polygonal and radially arranged parenchyma cells. Interspersed through these cells are solitary or pairs of crystal-bearing sclerenchyma fibers.

The phloem is difficult to distinguish from the cortex. However, it is made of several rows of thin-walled cells.

The cambium as in the stem is indistinguishable except as a line encircling the xylem.

The xylem is made up of a solid cylinder of lignified tissue which is composed of fibers and vessels. The fibers are arranged in radial rows of small quadrangular and polygonal shaped cells. The ducts appear as larger scattered isodiametric cells among the fibers.

In longitudinal section (Plate No. 8) there are four to nine rows of irregularly shaped, somewhat longitudinally elongated cork cells. The outer layers of cork cells are compact and difficult to distinguish individually.

Under the cork a region of approximately fifteen cells thickness is made up of longitudinally elongated polygonal parenchyma cells and scattered crystal bearing sclerenchyma fibers as is plainly shown in Plate No. 8.

The phloem and cambium are indistinguishable.

The xylem is made up of longitudinally elongated fibers, pitted tracheids and tracheal tubes.

SUMMARY AND CONCLUSIONS.

The flower heads, leaves, stems and roots of *Monarda punctata* **var.** *leucantha*, Nash., have been examined histologically. The histological examination substantiates the conclusions as to structures which were reached from macroscopical examination of the external features.

A NEW SUPPOSITORY BASE.*

BY JOHN C. BIRD.[1]

The following is an account of preliminary investigations in connection with a suppository mass more suitably adapted to the use of certain medicaments than, and without the disadvantages of, the more usual media.

Hippocrates (460–370 B. C.) used cathartic suppositories of salt, nitre and colocynth in a base or matrix of soap and honey. This type of medication, however, although popular in Europe for the last 200 years was not used in this country before about 1852 when Taylor (1) of Philadelphia described an opium suppository made with honey plasticized to the correct consistency by continued heating, and also with oil of theobroma which he found eminently satisfactory for the purpose. Cacao butter was given official recognition in the U. S. P. of 1860 and suppository data in general appeared in the pharmacopœias around 1864.

Since that time a great many alternative materials have been suggested as suppository bases, most of the earlier ones being mixtures of fats, waxes, glycerin, gums and soaps. Martindale (2) in 1890 stated that the glycerin and gelatin suppositories of that time were frequently discharged intact after 12 hours and put forward a mixture of stearic and oleic acids varying the proportions according to local temperature conditions. Most of these excipients, however, seem to have been regarded as merely a convenient means of introducing drugs into the rectum with apparently no regard to the modus operandi or ultimate fate of the medicament.

These aspects were appreciated and investigated by Lewin and Eschbaum (3), who recorded that, to be really effective, a drug must not only be very finely subdivided and evenly distributed in the matrix, but—and this is the important point—it must be easily separable therefrom. They investigated several excipients and concluded that neutralized agar agar was superior in these respects to all others then available.

More recently Terrey (4) has recommended a mixture of kaolin and decoction of Irish moss, while "Astra fat" (5) a hydrogenated arachis oil—also "Lipositoria" (6) a complex of cholesterin and sugar and several others all claiming to promote resorption have appeared in Germany.

THEORETICAL CONSIDERATIONS.

The ultimate aim of suppository medication may be systemic or local, and attention should therefore be paid to the type of action required and the means of insuring it. For systemic action the drug must be presented in readily absorbable form and should come into close contact with the mucosa. Aqueous solutions are of course most desirable in this respect so that it would seem illogical to apply water-soluble drugs to a watery membrane to be carefully insulated therefrom by a coating of wax, fat or oil as must obviously be the case with cacao butter.

When local action is required, as in the treatment of hemorrhoids and other rectal conditions, absorption may be secondary to a prolonged and intimate contact of the drugs with a smaller specific area.

It would seem equally unsound to adopt the same means for local treatment, as an aqueous or oily liquid cannot be expected to remain in one particular portion of the lower bowel. Overlach (7) appreciated this point and observed that the occasional failure to obtain satisfactory results from glycerin suppositories might be due to their escape so far into the rectum as to lose a large measure of efficiency. He suggested that the suppository be attached to a string having a small wooden handle at the distal end by which the location and duration of the medication might

* Scientific Section, A. PH. A., Dallas meeting, 1936.

[1] From the Division of Applied Research, Hoffmann-La Roche, Inc., Nutley, N. J.

be controlled. Such a device was actually patented in Germany although the extent of its practicability is not recorded.

Having these two main ideas of systemic and local actions in mind, much thought was given to the possibility of finding a suppository excipient which would most nearly fulfil both these requirements in addition to satisfying the many other minor but necessary conditions.

In view of the recent commercial availability of certain glyceryl and ethylene glycol esters of fatty acids with their excellent property of self emulsification, similar "synthetic fats" having free hydroxyl groups were investigated with a view to taking advantage of this characteristic.

Unfortunately the melting points of the mono glyceryl and ethylene glycol stearates and oleates were either much too high, or were of oily character, while admixture of other compatible low melting substances interfered largely with self emulsification and were unsatisfactory in other ways.

It was found, however, that the stearyl esters of α-propylene glycol possessed lower melting points and other favorable properties which rendered possible their adaptation to the purpose in view. By condensing the α-chlorhydrin of α-propylene glycol with sodium stearate the pure mono stearate is obtained after some manipulation. For larger scale production, however, the simpler method of direct condensation of the glycol with stearic acid is used. By using an excess of glycol and controlling the conditions the formation of distearate is kept at a minimum. The melting point of the pure distearate, however, is about 40° C. so that the presence of small quantities is of assistance rather than hindrance, the resultant melting point being just in the desirable range. A close check may be kept upon the progress of the esterification by frequent titration of samples with alcoholic potash, and the standardization is such that the characters of successive batches of material are practically identical. For convenience the term mono stearic ester of propylene glycol has been shortened to "monolene."

PROPERTIES OF "MONOLENE."

The stearic acid ester of α-propylene glycol as prepared for use as a suppository mass and using the best grade of commercial stearic acid is an ivory-colored, somewhat translucent wax-like solid, smooth and unguentous but not greasy to the touch, and with an agreeable odor reminiscent of cocoanut. It is of good consistency, amorphous when freshly prepared and cuts like firm cheese. It gradually changes in physical state on keeping, becoming more brittle and assuming a crystalline structure particularly evident upon fracture. This physical change common to many of the natural waxes and fats is accompanied by a rise in melting point.

The melting point of the fresh substance is from 33° to 34° C. rising after 24 hours or so to 35° C. On continued storage a maximum of 37° C. is reached in about three weeks after which no further change has been noticed during a period of six months. The congealing point of the aged material is 36° C.

It is soluble in the common organic solvents, *e. g.*, alcohol, chloroform, ether, acetone, benzol, etc., and in mineral and vegetable oils. It is immiscible with glycerin and the glycols.

The substance itself is hydrophilic in character, absorbing water to some extent. This property, as with the glyceryl esters, is enhanced by the presence of small quantities of the soaps of organic or inorganic bases. The melting point is but little affected by the addition of say 1–2% of sodium or ethanolamine stearate while the resulting product swells considerably in cold water, becoming completely self emulsified with the liquid as the continuous or external phase. The p_H of a 10% emulsion lies between 7 and 8.

As a suppository matrix it possesses several advantages. It congeals much more readily than cacao butter and may be "poured" at a higher temperature. Molds do not require nearly as much chilling while the shapes are removable with the greatest ease without external lubrication. The molded forms are of particularly fine and clean appearance having a firm bright surface of smooth lubricant quality, without sense of greasiness. This lubricant quality is greatly increased by slight wetting, thus rendering insertion of the suppository particularly simple and free from the objectionable features attendant upon cacao butter bases. Suppositories made from "Monolene" withstand warm weather better than cacao butter and do not give rise to as much spoilage in storing.

In contact with considerable water *in vitro* "Monolene" absorbs the liquid, swelling to several times its original size, eventually forming a soft creamy mass which on shaking or stirring becomes a hydrophilic plastic ointment (Fig. 1). This action is independent of temperature, for such swelling and ointment formation take place in ice water.

At body temperature the substance melts but at once emulsifies with any fluid present, such action being intensified under conditions of use by body or muscular movement. In the rectum or rectal canal the voluminous mass so formed may be expected to extend to the more inaccessible crypts and rugæ, or at least to provide more efficient contact with the mucosal walls (Fig. 2).

Being hydrophilic, such a substance should admit of the penetration and diffusion of aqueous fluids and consequent extraction of water-soluble medicaments more readily than would be possible from fats like cacao butter (Fig. 3). Absorption and efficiency of such drugs should be enhanced, while it is obvious that actual melting of the base is not essential to obtain the medication (Fig. 4).

A further advantage lies in the possibility of localizing certain insoluble drugs used in rectal treatment. Such drug particles are held by the mass in intimate contact with the walls in the desired area and are not widely distributed as with a free flowing non-emulsified fat, thus prolonging or intensifying treatment.

Oil-soluble medicaments, moreover, are applied in fine subdivision in the disperse phase of the emulsion. Schroff (8) recently showed that cacao butter emulsified with lecithin enabled absorption of water-soluble drugs to take place from the external water phase almost as quickly as by injection. By reversing the phases of the emulsion by cholesterol, more prolonged local action was possible.

PHARMACOLOGY.

Preliminary pharmacological tests have been directed toward ascertaining irritant or other undesirable effects of the base. Blank suppositories of small size were all retained by rabbits (starved for 24 hours previously) with no defecations until several hours later. Feces were soft, well formed and somewhat unctuous. No diarrhea, hyperemia or irritation of any kind was observed. These points were also confirmed by human tests.

Investigations as to drug absorption are still proceeding. Substances which give a recognizable effect upon blood pressure and respiration have been incorporated in "Monolene" and tests upon anesthetized animals recorded.

Observations to date show that water-soluble drugs are readily absorbed from this base—the effect of Sodium Alurate for example, in dosage sufficient to cause narcosis, exerted its effect in about 90 minutes. The same dose in an entirely fatty base took about 50% longer.

It is possible, of course, that differences in other cases may be less marked, and unqualified general superiority is by no means claimed as yet. It would seem, however, that in "Mono-

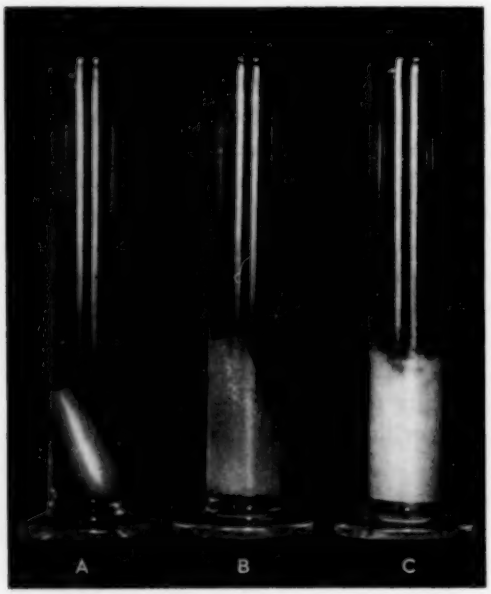

Fig. 1.—Water Imbibition at Room Temperature.

A. "Monolene" control—original size.
B. Suppository swollen in water.
C. Creamy mass after agitation.

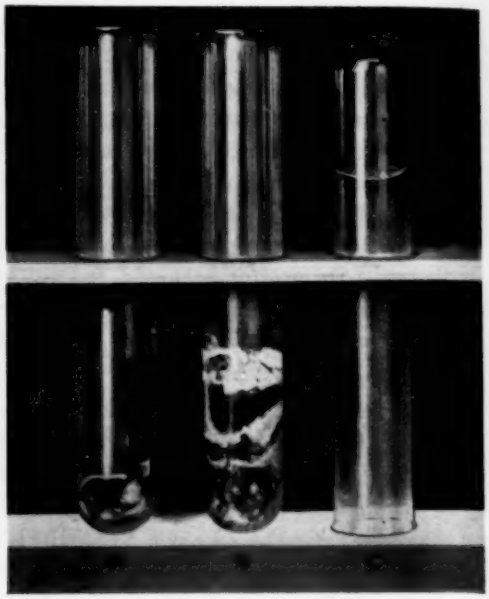

Fig. 2.—Action at Body Temperature.

A. Melted control.
B. Swollen mass in presence of water.
C. Showing firm but soft consistency.

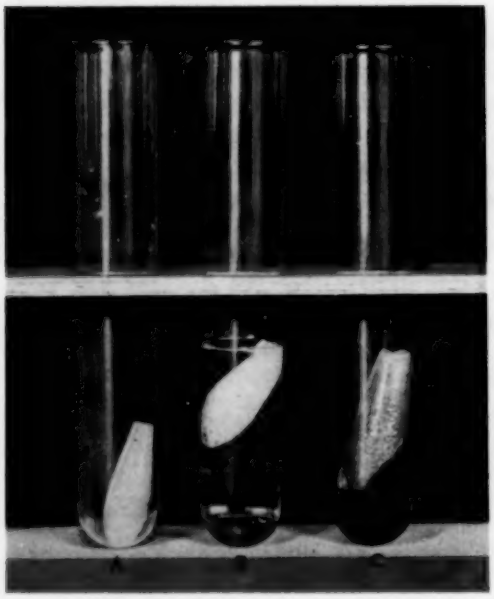

Fig. 3.—Extraction of Medicament by Diffusion.

A. "Monolene" control.
B. Cacao butter containing Congo Red powder, immersed in water.
C. "Monolene" under same conditions. Note extraction of dye, while cacao butter is impervious.

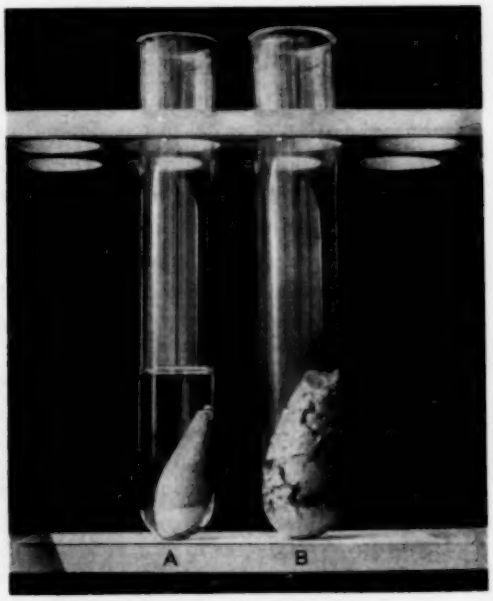

Fig. 4.—Action at Lowered Temperatures.

A. Cacao butter suppository in ice water in refrigerator several hours remains intact.
B. "Monolene" suppository disintegrates independent of temperature.

lene" we have a suppository medium whose physical properties render more likely the fulfilment of theoretical considerations of this type of medication, while providing many minor points of distinct advantage to both maker and user.

SUMMARY.

A new suppository base is suggested—propylene glycol stearate. The substance melts within body temperature range, is self emulsifying in water, forming soft, bulky, unguentous, hydrophilic and non-irritant emulsions particularly suitable for rectal treatment.

Its properties allow of medicament diffusion and absorption of water-soluble drugs irrespective of melting range, while insoluble substances are emulsified and kept in intimate local contact with mucosal tissue.

Other advantages include freedom from greasiness and leakage in use, while retaining firmness, ease and rapidity of molding, and better storage qualities.

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THE USE OF CETYL ALCOHOL AS AN ENTERIC COATING MATERIAL.*,[1]

BY LUCILLE M. MILLS.

The first reference to the passage of pills through the stomach undissolved was made by Proctor (1), in 1862, who ascribed the occasional failure of the pills to disintegrate either to the condition of the patient or the composition of the pill, rather than the nature of the coating. Wruble (2), in 1930, did some work on enteric coating materials; he stated, as a practical specification that an enteric coated tablet should withstand the gastric fluids for a period of four hours and then be deprived of its coat within one-half hour after entering the intestinal tract. Lozenski and Diver (3), used the fluoroscopic method to determine the point of disintegration. In their work they gave one tablet of barium sulfate and another of sodium salicylate, both having the same enteric coating. It was assumed that both tablets left the stomach at the same time; later this was shown to be a fallacy by Bukey and Brew (4).

The purpose of this study was to determine the value of cetyl alcohol, cetyl alcohol and shellac, and cetyl alcohol and mastic as possible enteric coating materials. Cetyl alcohol was chosen because of its similarity to some other coating materials which have been previously used with some success.

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* Scientific Section, A. PH. A., Dallas meeting, 1936.

[1] Study from the laboratories, College of Pharmacy, University of Nebraska.

EXPERIMENTAL PROCEDURE.

In these studies compressed tablets of barium sulfate were used. The granulation mass was made as follows:

Barium sulfate	50%
Starch	30%
Acacia	10%
Sugar	10%

This mass was then sent to a manufacturer who compressed it into tablets. Barium sulfate was used to render the tablets opaque to X-rays.

The tablets to be coated were placed in a rotating metallic hopper and a small amount of the coating material was sprayed on the side of the hopper so as not to moisten the tablets. As the tablets rotated they were coated. More coating was added from time to time, as the coating dried due to the evaporation of the solvent. A small amount of purified talc was added to give body to the coat and when the coating was uniform the tablets were removed from the hopper and allowed to dry.

The cetyl alcohol, or the various combinations of cetyl alcohol and other materials used, were dissolved in acetone so that the material could be sprayed over the tablets.

The coated tablets were administered to students, and the time and point of disintegration was determined by means of radiographs. The students were chosen at random so that a cross section of various types of individuals could be studied. Since tablets are given for various reasons and under widely differing conditions we were endeavoring to find a material suitable for enteric tablets which might be given for any condition for which the physician wished to prescribe.

The first series of tablets were coated with a cetyl alcohol coating; other tablets were coated with a cetyl alcohol-shellac coating and still others with a cetyl alcohol-mastic coating. The following chart gives the number of grams of the ingredients used.

TABLE I.

Ingredients.	Group I.	Group II.	Group III.
Cetyl alcohol	10 Gm.	10 Gm.	10 Gm.
Shellac		10 Gm.	
Mastic			10 Gm.
Acetone	100 cc.	100 cc.	100 cc.

The shellac was added to the cetyl alcohol as it was thought that it would give body to the coating. Shellac had been previously studied and found unsatisfactory as a coating material when used alone. Wruble (2) suggested that the value of shellac as a coating material might be due to the fact that it is produced from an animal source (*Tachardia lacca*).

EXPERIMENTAL DATA.

The following abbreviations and symbols are used in the charts. *S*, stomach; *S. I.*, small intestine; *A. C.*, ascending colon; *T. C.*, transverse colon; and *D. C.*, descending colon. *Loc.* unknown, exact point of disintegration is unknown.

The calculations used in determining the efficiency of the enteric coating were made as follows. The number of tablets for which the point of disintegration was unknown was deducted from the total number of tablets given, and this value used as the denominator in the efficiency factor. The numerator was determined by subtracting from the total number of tablets used those disintegrating in the stomach, the number remaining in the stomach at the end of the experiment, and those in which the point of disintegration was unknown.

CETYL ALCOHOL COATING.

TABLE II.

Time and Point of Disintegration.

Hours.	4.	5.	6.	7.	8.	10.	11.	12.	Total.
S.	2		2	3				1	8
S. I.	3	1	1	5			3		13
A. C.	1	1	2	1	1	3	13		22
Loc. unknown						4	4		8
Total									51

Location and Time of Those Tablets Not Disintegrating.

S.			1	2				6	9
S. I.			7	1	1		7		16
A. C.			1	9	4		5	1	20
T. C.						2			2
Total									47

Total number of tablets used was 98.
Number of subjects was 25.
Efficiency was 81.11 per cent.

TABLE III.—CHART FOR DETERMINING EFFICIENCY OF COATINGS.

For Denominator.	Cetyl Alcohol Coating.	Cetyl Alcohol-Shellac Coating.	Cetyl Alcohol-Mastic Coating.
Total number tablets	98	85	47
Disintegration point unknown	8	3	0
Total	90	82	47
For Numerator.			
Disintegrating in *S*	8	11	0
Not disintegrating in *S*	9	16	1
Loc. unknown	8	3	0
Total not considered	25	30	1
Total number tablets	98	85	47
Total not considered	25	30	1
Total	73	55	46
Efficiency	$\frac{73}{90} \times 100 =$ 81.11%	$\frac{55}{82} \times 100 =$ 70.73%	$\frac{46}{47} \times 100 =$ 97.98%

It will be noted that nine tablets remained in the stomach at the time when the last radiograph was taken. Some of these may have passed into the intestinal tract but as no definite evidence could be obtained it was thought best to omit this number. It is obvious that the efficiency might be greater than the value reported. The tablets in the disintegration chart marked location unknown have no bearing on the value since it was deducted from both numerator and denominator.

CETYL ALCOHOL-SHELLAC COATING.

TABLE IV.

Time and Point of Disintegration.

Hours.	4.	5.	6.	8.	11.	Total.
S.	1	6	2	2		11
S. I.	16	13	11	3	2	45
A. C.		4	2			6
Loc. unknown	1		2			3
Total						65

Location and Time of Those Tablets Not Disintegrating.

S.	2	14	16
S. I.		4	4
Total			20

Total number of tablets used was 85.
Number of subjects was 20.
Efficiency was 70.73 per cent.

In making the calculations for the efficiency of this coating the same procedure was used as in the previous study. For calculations see Table III.

CETYL ALCOHOL-MASTIC COATING.

TABLE V.

Time and Point of Disintegration.

Hours.	4.	5.	6.	7.	8.	10.	11.	12.	Total.
S.									0
S. I.									0
A. C.	1			1			1	4	7
Total									7

Location and Time of Those Tablets Not Disintegrating.

S.					1		1
S. I.		4	1	3	1		9
A. C.			6	5	4	5	25
T. C.						2	2
D. C.						3	3
Total							40

Total number of tablets used was 47.
Number of subjects was 13.
Efficiency was 97.87 per cent.

The calculations were made in the same manner as the preceding. See Table III.

CONCLUSIONS.

From this study the following conclusions may be drawn:

(1) That cetyl alcohol as an enteric coating material was 81.11 per cent efficient.

(2) That cetyl alcohol-shellac as an enteric material was 70.73 per cent efficient.

(3) That cetyl alcohol-mastic as an enteric coating material was 97.87 per cent efficient.

(4) That in the case of cetyl alcohol-mastic coating the highest percentage of the tablets disintegrated in the ascending, the transverse and descending colon.

(5) That the efficiency of the cetyl alcohol-mastic coating can be increased by decreasing the amount of mastic used in the preparation of the coating mixtures.

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THE RELATION OF BARBITAL AND PHENOBARBITAL TO GRANULOCYTOPENIA.*

BY J. C. KOPET AND F. J. GOODRICH.

Evidence obtained by reviewing the literature indicates that amidopyrine is an important factor in the production of granulocytopenia. Since barbituric acid derivatives are commonly prescribed with amidopyrine, and since the cause of many of the cases of syndrome have been traced to certain proprietary combinations of amidopyrine and barbituric acid derivatives, it might be expected that barbiturates could be responsible for the causation of a decrease of granulocytes in peripheral blood. An investigation was conducted to clarify the rôle of the barbiturates in the experimental production of granulocytopenia. The question of whether the presence of a barbiturate with amidopyrine results in a synergistic action, or otherwise influences the effect of amidopyrine remains to be determined.

Agranulocytosis was first named and described by Schultz (2) in 1922. Kracke (3) reported that the term granulocytopenia more correctly expressed the actual condition existing in that disease known more commonly as agranulocytosis than any that has been suggested. The name of granulocytopenia is consistent with the accepted nomenclature describing variations in numbers and percentages of white blood cells and denotes a decrease in granular cells. The term "agranulocytic angina" should be abandoned as many of the patients having a definite granulocytopenia have shown no oral lesions.

Granulocytopenia seems to be a disease which may be acute or chronic, severe or mild, depending upon the extent to which the granular cells are decreased. The condition known as agranulocytosis, meaning "an increase in the number of immature granular cells," is probably the most extreme state of the disease in which the granular cells almost completely disappear from peripheral blood; this, in turn, being followed by local or general sepsis and usually by death. Agranulocytosis is apparently a disease entity in which an unknown agent produces a depression of the bone marrow, this resulting in loss of neutrophilic resistance with subsequent overwhelming infection in those areas of the body normally inhabited by bacteria. The type of case which is characterized by loss of neutrophiles and death without evidence of infection is also classified as agranulocytosis.

Kracke (3) felt that the peculiar distribution of granulopenia could well be correlated with the use of certain drugs containing the benzene ring which are commonly used for therapeutic purposes. Benzene poisoning has been recorded as a process in which hematopoieses is completely inhibited in all of the three bone marrow elements. Certain drugs of the coal-tar series have been constantly associated with cases of granulocytopenia. Kracke points out that these drugs all have as a nucleus the benzene ring with an attached amine ($-NH_2$) group, making them substituted primary amines. This basic structure sets them apart as far as their reactions are considered from other coal-tar derivatives, such as aspirin, and the like, which do not contain the primary amine. For this reason, he has arbitrarily designated these compounds as "benzamine drugs" to facilitate reference to them as a group. The drugs contained in this group are amidopyrine, phenacetin, acetanilid and arsphenamine.

Amidopyrine appears on the market in proprietary compounds containing it and a barbiturate and is commonly prescribed this way. In many cases of granulocytopenia, this type of sedative had been administered previous to the appearance of the clinical picture of the disease, and it could not be stated definitely that either amidopyrine or the barbiturate alone was responsible for the condition.

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* Scientific Section, A. PH. A., Dallas meeting, 1936.

EXPERIMENTAL.

Barbital (diethyl barbituric acid) and phenobarbital (phenyl ethyl barbituric acid) were administered to rabbits in an attempt to produce granulocytopenia experimentally. Barbital was used because it consisted of two straight chain groups linked to the malonyl-urea group, and phenobarbital was administered because it contained a benzene group substituted for an ethyl group of barbital. In this way it might be possible to indict either the barbituric acid nucleus or the phenol group, if a condition of granulocytopenia could be produced in either case.

Since the interest lay in determining whether or not a daily administration of the drug, rather than an acute poisoning, could produce a decrease in granulocytes, no change in the amount administered was made during the period that the animals were subjected to the experiment. It was decided to administer orally an amount equal approximately to one-half of the minimum lethal dose of the drug for the body weight of the animal. There was a possibility that the accumulation of the drug in the blood stream could cause a poisoning, since the barbiturates are excreted slowly, but this in itself might cause a condition of granulocytopenia, which was the object of the experimentation. Taking 300 mg. (4.626 grains) per Kg. of body weight as being nearly the minimum lethal dose for barbital, it was decided to administer 5 grains (0.324 Gm.) to the rabbits weighing 2 Kg. In a like manner, 1.5 grains (.098 Gm. of phenobarbital were selected as a convenient dose for 2-Kg. rabbits, since the M. L. D. is approximately 100 mg./Kg. It is merely coincidental that the amount of these doses correspond to the average human dose.

The drug was administered orally to allow the substance to undergo any changes in the alimentary tract that might alter its toxicity before absorption, since, as it has been explained previously, there is a suspicion that the harmful effect of the benzamine class of drugs is due to various derivatives that might be formed within the body. Such could possibly be the case with the barbiturates. It would not be right to seek to obtain data from the effect of hypodermic administration of the substances when the majority of the cases of granulocytopenia from chemicals were traced to the oral administrations. Furthermore, these particular barbiturates are universally prescribed to be taken orally. A total white cell count was performed following the daily oral administration of the drugs and a differential count was also obtained. For convenience, the differential count was recorded on the basis of granulocytes and nongranulocytes; polymorphonuclear neutrophiles, basophiles and eosinophiles being classed as granulocytes, and the lymphocytes and monocytes falling into the other classification. The total number of granulocytes was obtained by calculation from the total white cell count and the percentages obtained by the differential count.

SUMMARY.

1. Granulocytopenia is a condition of a decreased number of circulating granulocytes in the peripheral blood, probably affected by a chemical agent causing the bone marrow to fail to produce granulocytes.

2. Drugs similar to amidopyrine, having an amine group attached to a benzene group in their structural formula, are apparently the cause of this condition.

3. Barbital and phenobarbital do not cause a permanent decrease in the number of circulating granulocytes in the peripheral blood of normal rabbits.

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A STUDY OF METHYLENEDISULFONIC ACID AND ITS DERIVATIVES.*

BY JOHN C. BAUER[1] AND GLENN L. JENKINS.

Chemotherapeutic studies of the barbital and sulfonal groups of hypnotics have established definitely a relationship between their chemical structure and their therapeutic action.

The two drugs, barbital and sulfonal, may be considered the precursors of two important series of hypnotics, the methylenedisulfonic acid group and the malonylureide group. The chemotherapeutic concepts of these compounds undoubtedly link their physiological activities with their characteristic molecular structures, and it would seem rational to conceive of a compound having a structure which included the hypnophore groups of both of these series. The basic structure of such a barbituric acid sulfonal hybrid would be $\underset{\_\_\_\_\_}{\text{:C—SO}_2\text{.NH.CO.NH.SO}_2}$, and the relation of methylenedisulfonic acid to it would be analogous to the relation of malonic acid to the barbiturates.

A survey of the literature revealed only one attempt to prepare such a hybrid compound, and this was unsuccessful and offered little encouragement to future investigators. However, the synthesis and pharmacological study of such a series of compounds would add much information to our present knowledge of the chemotherapy of hypnotics, and might result in the production of some valuable therapeutic agents. The work reported here has as its object the study of the problems involved in the preparation of derivatives of methylenedisulfonic acid and as its hope the preparation of the hybrid methylenedisulfonureide structure shown above.

EXPERIMENTAL.

The basic compound methylenedisulfonic acid has been prepared by Schroeter (1) who obtained it as its barium salt in yields of 15 per cent and by Backer (2) who obtained it as the potassium salt in yields of 85 per cent.

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* Scientific Section, A. PH. A., Dallas meeting, 1936.

[1] Abstracted, in part, from a thesis submitted by John C. Bauer to the Faculty of the Graduate School of the University of Maryland in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

Preparation of Potassium Methylenedisulfonate (*2*).—One mol. (85 Gm.) of methylenechloride was bombed for two hours with 400 Gm. of potassium sulfite dissolved in 350 cc. of water at a temperature of 150° to 160° C. and a pressure of about 20 atmospheres. Constant stirring is essential. The reaction product, which was completely free of methylenechloride, consisted of a large quantity of crystalline material and an aqueous solution. The crystals were dissolved in the aqueous solution by boiling and filtered while hot. The potassium methylenedisulfonate, which is soluble 4 parts in 100 of cold water, immediately began to crystallize out in the filtering flask, and when cold the filtrate yielded a large quantity of the compound. The product was recrystallized from hot water, and 75 per cent of the theoretical yield of the potassium salt was obtained as large prismatic crystals. The compound was dried and identified by converting it into the barium salt.

	Wt. of Sample.	Wt. of $H_2C(SO_3)_2Ba.2H_2O$.
Calculated for $H_2C(SO_3K)_2$	4.6 Gm.	6.4 Gm.
Observed	4.6 Gm.	6.3 Gm.

The barium salt was dried *in vacuo* at 105° C. to eliminate all of its water of hydration and identified by analyzing for barium.

	Wt. of Sample.	Wt. of Barium.	Per Cent of Barium.
Calculated for $H_2C(SO_3)_2Ba$	0.3873 Gm.	0.1709 Gm.	44.13
Observed	0.3873 Gm.	0.1721 Gm.	44.43

Preparation of Barium Methylenedisulfonate.—A hot concentrated solution of barium chloride was added to a hot solution of potassium methylenedisulfonate which had been acidified with hydrochloric acid. Barium methylenedisulfonate separated from the cooled reaction mixture as small white crystalline plates, having a silvery luster; 363 Gm. of potassium methylenedisulfonate yielded 489 Gm. of barium methylenedisulfonate. A portion of this barium salt was purified by recrystallization from hot water. The resulting product was insoluble in chloroform, alcohol and cold water, and only sparingly soluble in hot water. Thus it is apparent that the water solubility of this compound parallels barium sulfate more closely than it does the barium alkylmonosulfonates. When heated strongly the crystals fused, charred with the evolution of sulfur dioxide, and left a white residue of barium sulfate.

A sample of the purified barium methylenedisulfonate was dried at 105° C. and placed in a desiccator over sulfuric acid to determine the loss of water of hydration. Drying was continued for thirty days and weighings were made at five-day intervals.

	Wt. of Sample.	Loss in Wt.	Per Cent Loss in Wt.
Calculated for $H_2C(SO_3)_2Ba.2H_2O$ giving $H_2C(SO_3)_2Ba.H_2O$	0.7159 Gm.	0.0371 Gm.	5.18
Observed	0.7159 Gm.	0.0365 Gm.	5.10

This dried material was analyzed for barium.

	Wt. of Sample.	Wt. of Barium.	Per Cent of Barium.
Calculated for $H_2C(SO_3)_2Ba.H_2O$	0.0493 Gm.	0.0206 Gm.	41.78
Observed	0.0493 Gm.	0.0206 Gm.	41.78

Drying at 120° C. also removes one molecule of water of hydration and, as shown by a preceding analysis, at 105° C. *in vacuo* the unhydrated salt is formed.

Preparation of Methylenedisulfonic Acid.—While boiling and stirring, 500 Gm. of barium methylenedisulfonate were added in 5- to 10-Gm. portions to 141 Gm. of concentrated sulfuric acid dissolved in 2 liters of water. After adding all of the barium salt, boiling and stirring were continued until 2 drops of the filtered reaction mixture when diluted to 10 cc. and treated with barium chloride gave no precipitate of barium sulfate. The barium sulfate was removed from the reaction mixture by suction filtration and the filtrate, which contained the methylenedisul-

fonic acid, was concentrated until the temperature of the boiling solution reached 132° C. Drying was completed by heating in an oven for fourteen hours at 153° C. under reduced pressure. Upon cooling, 253 Gm. of a white crystalline product were obtained. Based on the assumption that it was 95 per cent pure (1), the yield was 94.6 per cent.

This is essentially the method described by Schroeter (1) with certain modifications which in our hands permitted us to obtain greater yields of a cleaner product.

Methylenedisulfonic acid is extremely hygroscopic and if the crystalline substance is exposed to air it rapidly absorbs water and dissolves.

Preparation of Methylenedisulfonylchloride.—Phosphorus pentachloride was added in small portions to 250 Gm. of the crystalline methylenedisulfonic acid during a period of 50 hours. The stratified solid reaction mixture was warmed sufficiently to start the reaction. After the initial heating required to start the reaction, no heat was applied and the phosphorus pentachloride was added in small portions to prevent overheating. When no more solid methylenedisulfonic acid remained, the excess phosphorus pentachloride was removed by filtering the reaction mixture through glass wool. Further purification was effected by fractional distillation. The phosphorus oxychloride was removed by distilling on a steam-bath under 150-mm. pressure. The residual heavy oil was distilled under 15-mm. pressure and the methylenedisulfonylchloride was collected in the fraction which distilled between 120° C. and 140° C.; 256 Gm. of the product were collected which corresponds to a yield of 89 per cent. When purified by repeated fractionations a clear, colorless, heavy oil was obtained, b. p. 135° to 138° C. at 15-mm. pressure, sp. gr. 1.824 at 19° C. The oil is not decomposed by cold water or alcohol, but rapidly forms methylenedisulfonic acid when warmed with these substances.

The procedure, which is also a modification of the method described by Schroeter (3), permitted us to obtain larger yields.

An effort was made to prepare this compound using sulfonylchloride in place of phosphorus pentachloride, but no methylenedisulfonylchloride could be isolated from the reaction mixture.

Alkylesters of methylenedisulfonic acid could not be prepared from methylenedisulfonylchloride and an aliphatic alcohol, but were obtained by refluxing the dry silver salt of methylenedisulfonic acid with an anhydrous benzene solution of an alkyliodide (4).

Preparation of Silver Methylenedisulfonate (3).—A solution of methylenedisulfonic acid was prepared by decomposing 237 Gm. of barium methylenedisulfonate with 36 cc. of concentrated sulfuric acid dissolved in 360 cc. of water. The reaction mixture was filtered and the filtrate, which contained the methylenedisulfonic acid, was added to a slight excess of freshly precipitated silver carbonate. When there was no further evolution of carbon dioxide the reaction mixture was filtered, concentrated to a small volume, cooled and diluted with an equal volume of alcohol. The silver methylenedisulfonate precipitated out as a white crystalline product which was dried in a vacuum desiccator and finally in an oven at 104° C. A yield of 227 Gm. (91 per cent) was obtained.

Preparation of the Dimethylester of Methylenedisulfonic Acid (4).—19.5 Gm. of the finely powdered silver salt which had been dried at 104° C. for 20 hours was treated with 10 cc. of methyliodide which had been dried over calcium chloride and freed of iodine by shaking with mercury. Ten cc. of anhydrous benzene were added and the mixture refluxed for 3 days. Additional benzene and small volumes of methyliodide were added occasionally. The reaction mixture was filtered hot and the residue extracted with several portions of hot benzene. The filtrate and extractions were united and concentrated. When cool 7.8 Gm. (76.5 per cent) of the dimethylester were obtained, m. p. 47.5° C.

The procedure for preparing the dimethylester as described here varies considerably from that described by Schroeter (3), however, we obtained excellent results using the above method.

As reported by Schroeter (3), the compound was found to be unstable when warmed with water or alcohol. Water decomposes it into the free acid and alcohol, and warm alcohol produces the free acid and ether. When boiled in alcoholic solution, good yields of ether are obtained. This property of the compound to form ether when boiled with alcohol is not in accord with the usual behavior of the esters of alkylcarboxylic acids, but is quite analogous to the behavior of sulfuric acid in the preparation of diethylether, and probably explains why the alkylesters of methylenedisulfonic acid cannot be prepared from methylenedisulfonylchloride. In confirmation of an observation made by Schroeter (4), we noted that the free acid was efficient in the synthesis of the higher molecular weight ethers and succeeded in obtaining a large yield of di-isoamylether by distilling a mixture of the acid and isoamyl alcohol.

The methylene hydrogen atoms of the alkylesters can be replaced by sodium or potassium but not as readily as in the case of the arylester. Contrary to the findings of others (5), we were unable to alkylate the methylene carbon atom.

Arylesters of Methylenedisulfonic Acid.—The diphenylester was prepared by Schroeter (5) by refluxing a toluene solution of methylenedisulfonylchloride and phenol for 20 hours. Recently Raschig and Prahl (6) described a more efficient method of preparing this compound.

Preparation of the Diphenylester of Methylenedisulfonic Acid (6).—21.3 Gm. of methylenedisulfonylchloride were dissolved in 100 cc. of benzene and cooled to 0° C. While shaking and cooling this solution was added to a solution containing 17.8 Gm. of phenol and 30 cc. of pyridine in 100 cc. of benzene which had also been cooled to 0° C. The reaction mixture was decomposed with ice and shaken out with dilute hydrochloric acid and water. When all of the pyridine had been removed, the diphenylester was shaken out into a warm 2*N* sodium hydroxide solution. The diphenylester can be isolated from this alkaline solution in a number of ways. We diluted the alkaline extract, acidified with hydrochloric acid and obtained 21 Gm. of the diphenylester of methylenedisulfonic acid which, after recrystallization from alcohol, melted at 82° to 83° C. (uncorrected) (5).

This compound is soluble in ether, benzene, chloroform, hot alcohol and hot carbontetrachloride. The methylene hydrogen atoms can be replaced by sodium or potassium by adding the alkali metal to an anhydrous toluene or alcoholic solution of the ester, or by treating it with aqueous sodium or potassium hydroxide. These metal derivatives are insoluble in benzene and alcohol and they undergo reactions analogous to the alkali metal derivatives of the malonic acid esters.

Amides of Methylenedisulfonic Acid.—Similarly to the esters, the aryl and alkyl amides must be prepared by different methods.

Preparation of the Dianilide of Methylenedisulfonic Acid (3).—0.1 mol of methylenedisulfonylchloride was dissolved in 100 cc. of benzene and cooled in an ice-water mixture. While stirring, a cold benzene solution containing 0.4 mol of aniline was added slowly, and when the reaction had subsided, the mixture was refluxed for 30 minutes. The methylenedisulfonanilide was shaken out into warm 2*N* sodium hydroxide as the *N*-sodium derivative. After washing with several portions of benzene, the aqueous solution was acidified with concentrated hydrochloric acid and the precipitated anilide was collected on a suction filter. By crystallization from hot alcohol 25 Gm. (77% of the theoretical yield) of anilide, m. p. 192° to 193° C., were obtained. The compound was analyzed for sulfur.

	Wt. of Sample.	Wt. of $BaSO_4$.	Per Cent of Sulfur.
Calculated for $H_2C(SO_2NH.C_6H_5)_2$	0.1372 Gm.	0.1963 Gm.	19.65
Observed	0.1372 Gm.	0.1963 Gm.	19.65

As previously reported by others (3) amides of secondary amines containing at least one aryl group were prepared by the same method in good yields.

The amide hydrogen atoms of the secondary amides of methylenedisulfonic acid impart acidic properties to the compounds so that they react with aqueous sodium and potassium hydroxide to form soluble products. These hydrogen atoms can also be replaced by metallic sodium or potassium in alcoholic or benzene medium. The tertiary amides of methylenedisulfonic acid contain no amide hydrogen, but the hydrogen atoms attached to the methylene carbon atom can be replaced by metallic sodium or potassium when the reaction is carried out in anhydrous alcohol or benzene. The reactions with the alkali metals are of importance in the synthesis of derivatives of these compounds.

Preparation of Methylenedisulfonamide (3).—A cold benzene solution containing 33 Gm. of the diphenylester of methylenedisulfonic acid was saturated with dry ammonia gas. Toward the end of the reaction two immiscible liquid layers formed. This mixture was transferred to a bomb and heated for four hours between 140° and 145° C. A benzene insoluble crystalline material was obtained which, when recrystallized from hot water, yielded 12.7 Gm. (73 per cent of the theoretical yield) of the diamide, m. p. 232° to 233° C. (uncorrected).

The compound is insoluble in alcohol, benzene, glacial acetic acid and water, but forms water-soluble *N*-sodium and potassium compounds analogous to the secondary aryl- and alkylamides of methylenedisulfonic acid.

Other efforts to prepare this amide include the following methods: The passing of dry ammonia into an anhydrous benzene solution of methylenedisulfonylchloride, the passing of dry ammonia into an anhydrous benzene solution of methylenedisulfonylchloride and pyridine, the slow distillation of a solution of ammonium methylenedisulfonate in glacial acetic acid, and the passing of dry ammonia into an anhydrous solution of methylenedisulfonic acid dimethylester in benzene. Reactions occurred in all of these experiments and the products were isolated and identified by analysis but in no case was any amide obtained. The method in which ammonia was permitted to react with the dimethylester of the acid was interesting, since it yielded the ammonium salt of methylenedisulfonic acid and methylamine. This result is quite contrary to the reaction which occurs when the methylesters of carboxylic acids are treated in this manner but directly analogous to the reaction which occurs when dimethylsulfate is treated with ammonia under the above conditions.

Alkyl substitution of the methylene hydrogen atoms: Schroeter was the first to effect this synthesis using a method similar to the malonic acid synthesis (3). He reported that when the monosodium derivative of methylenedisulfonic acid diphenylester, $Na.HC(SO_2OC_6H_5)_2$, made by treating a solution of methylenedisulfonic acid diphenylester in anhydrous benzene with sodium, was treated with an alkyliodide or sulfate, the monoalkyl derivative was formed $R.HC(SO_2OC_6H_5)_2$. The second hydrogen atom of this monoalkylated compound likewise can be replaced by sodium, but the subsequent addition of alkyliodide or alkylsulfate may or may not yield the dialkyl derivative. If the first radical introduced is a methyl group, the second radical readily attached itself to the methylene carbon atom, but if the first radical introduced is not a methyl group, then disubstitution cannot be effected except when the resulting compound would be methylalkylmethylenedisulfonic acid diphenylester. Thus the dialkyl derivatives which have been syn-

thesized are limited to methyl ethyl, methyl propyl, etc., and the only symmetrical dialkyl derivative which has been made is dimethyl.

We prepared the alkyl substituted derivatives by a modification of the Schroeter method and succeeded in obtaining the dimethylmethylenedisulfonic acid diphenylester by a single treatment with sodium followed by complete alkylation.

Preparation of Dimethylmethylenedisulfonic Acid Diphenylester.—Five Gm. of powdered sodium were prepared in 50 cc. of anhydrous toluene, and when the mixture had cooled, 0.1 mol. (33 Gm.) of the diphenylester of methylenedisulfonic acid dissolved in 250 cc. of anhydrous toluene was added. When the evolution of hydrogen became sluggish, the temperature of the reaction mixture was raised to boiling and refluxing was continued until practically all of the sodium had disappeared. The disodium derivative separated as a white voluminous precipitate. After cooling, 0.3 mol. (14.5 cc.) of freshly distilled dimethylsulfate was added and the temperature of the mixture was raised gradually to boiling. After refluxing for ninety minutes the voluminous precipitate was replaced by a heavy precipitate of sodium methylsulfate which was filtered off. The toluene was removed from the filtrate by distillation under reduced pressure and the residual impure diphenylester of dimethylmethylenedisulfonic acid was purified by crystallization from hot carbontetrachloride. The method yielded 26 Gm. (73%) of the dimethyl derivative, m. p. 95° to 97° C. (uncorrected). The compound was analyzed for sulfur.

	Wt. of Sample.	Wt. of $BaSO_4$.	Per Cent of Sulfur.
Calculated for $(CH_3)_2C(SO_2OC_6H_5)_2$	0.2761 Gm.	0.3614 Gm.	17.98
Observed	0.2761 Gm.	0.3622 Gm.	18.02

The tertiary arylamides of methylenedisulfonic acid, such as the diethylanilide, may also be used for alkylation of the methylene carbon atom, but the primary and secondary anilides form *N*-alkyl derivatives as the result of the greater activity of the amido hydrogen atoms. Schroeter attempted to overcome this difficulty by acetylating the amide groups but found that the resulting compounds were not acted upon by metallic sodium. Schroeter (3) prepared the dialkyl derivatives of these anilides using anhydrous benzene as the solvent and reported that the intermediate sodium derivatives were readily decomposed by alcohol. However, we had greater success in the preparation of these compounds when anhydrous alcohol was added to the reaction mixture, but in no case did we obtain yields as great as those reported by Schroeter.

Preparation of Monomethylmethylenedisulfonethylanilide.—Two and five hundredths Gm. of sodium were permitted to react with 50 cc. of anhydrous alcohol which had been freshly distilled from sodium. Thirty-four Gm. of methylenedisulfonethylanilide dissolved in 150 cc. of anhydrous benzene were added and the reaction mixture was refluxed for one hour. Upon the addition of 10 cc. of methyliodide a reaction took place immediately as evidenced by the precipitation of sodium iodide. After refluxing for thirty minutes the sodium iodide was removed by filtration and by shaking out the filtrate with water. The benzene and alcohol were distilled off and the residue when cooled yielded 28.5 Gm. of crude product which when purified by crystallization from alcohol yielded 25.5 Gm. (72 per cent) of pure monomethylmethylenedisulfonethylanilide, m. p. 150° to 152° C. (uncorrected) (3).

Preparation of Dimethylmethylenedisulfonethylanilide.—One and one-tenth Gm. of sodium were permitted to react with 5 to 7 cc. of anhydrous alcohol which had been freshly distilled from sodium. Heat was required to complete this reaction. 12.5 Gm. of monomethylmethylenedisulfonethylanilide dissolved in 150 cc. to 200 cc. of anhydrous benzene were added and the reaction mixture was refluxed for one hour during which time a flocculent precipitate was formed; 8 cc. of methyliodide were added and refluxing continued for three hours. The solvent was removed by distillation and evaporation and the thick sirupy residue cooled. When this was stirred with cold alcohol it set to a crystalline mass which, after washing on a suction filter with

hot water followed by cold alcohol, yielded 12.5 Gm. of crude product, m. p. 114° to 118° C. When purified by fractional crystallization from hot alcohol a yield of 4.5 Gm. (35 per cent) of dimethylmethylenedisulfonethylanilide was obtained, m. p. 132° C. (uncorrected) (3) and 4.2 Gm. of the unchanged monomethyl derivative, m. p. 150° to 152° C. (uncorrected) were recovered.

The use of the alkylesters of methylenedisulfonic acid in the synthesis of these alkyl substituted derivatives is of questionable value. Schroeter (3) reported that the methylene hydrogen atoms of the alkylesters could be replaced by sodium but that the reaction was sluggish, and he succeeded in preparing the monoethyl derivative in poor yields by this means. All attempts in our laboratory to prepare either the mono- or dialkyl substituted derivatives produced either no yields of the expected product or quantities too small to be used for synthetic studies.

Hydrolysis of the Arylesters or Anilides of Methylenedisulfonic Acid and Its Alkyl Derivatives.—These compounds are characterized by their stability in boiling acids and alkalies. To saponify methylenedisulfonic acid diphenylester or its monoalkyl derivative it is necessary to boil them for four hours with 50 per cent potassium hydroxide solution (5) or to heat them four hours at 140° to 145° C. with a 4 per cent alcoholic solution of ammonia. Prolonged boiling with either sodium ethoxide or nitric acid is ineffective (5). The diethylanilides of these compounds are likewise very stable to alkalies but are hydrolyzed by heating for two hours with 15 per cent hydrochloric acid at 150° to 200° C. (5). The dialkyl derivatives are even more resistant to hydrolysis and cannot be split by acids, but when heated for seven hours with an alcoholic solution of sodium methylate at 150° to 160° C. one of the sulfonic acid groups is split off leaving the salts of the corresponding dialkyl-alpha hydroxy-methylmonosulfonic acids (5).

If our hope of preparing a hybrid sulfonal barbital compound was to be realized, it was essential to find a method of hydrolyzing these dialkylated arylesters or anilides and a number of experiments were directed toward hydrolyzing the diphenylester of dimethylmethylenedisulfonic acid.

Method 1—3.0 Gm. of the compound when bombed with dry ammonia in anhydrous ether for three hours at 150° C. under a pressure of 21 atmospheres yielded none of the desired ammonium salt, and 2.8 Gm. of the original ester were recovered and identified.

Method 2—1 Gm. of the compound when fused for four hours with 10 Gm. of urea yielded none of the desired ammonium salt or ureide, and 0.81 Gm. of the original ester was recovered and identified.

Method 3—1.5 Gm. of the compound when refluxed for three hours with 2 Gm. of aluminum chloride in carbondisulfide yielded none of the desired aluminum salt, and 1.3 Gm. of the original ester were recovered and identified.

Method 4—Experiment 3 was repeated substituting 30 cc. of concentrated hydrochloric acid for the carbondisulfide but again the original ester was recovered quantitatively and identified.

Method 5—3.5 Gm. of the compound, when bombed for four hours under 10 atmospheres of pressure with 38.8 Gm. of potassium sulfite and 10 Gm. of potassium hydroxide in 200 cc. of water, yielded none of the desired potassium salt, however, the original ester could not be identified in the reaction product.

Recently Schroeter reported (7) that when 3.56 Gm. of the dialkylated diphenylester was bombed for fourteen hours at 210° C. with an equimolar quantity of barium hydroxide in alcoholic solution it yielded 0.2 Gm. of the desired barium salt $(CH_3)_2C(SO_3)_2Ba$, and 4.1 Gm. of the dialkylated diethylanilide under similar

conditions yielded 2.3 Gm. of the desired barium salt. We were unable to hydrolyze the diethylanilide to the corresponding barium salt by this procedure.

Cyclic Ureides of Methylenedisulfonic Acid and Its Derivatives.—Two series of experiments were carried out in an effort to prepare these cyclic ureides, one in which attempts were made to condense urea with the disulfonylchloride,

$$:C(SO_2Cl)_2 + H_2NCO.NH_2 \longrightarrow :C\underline{\text{—}SO_2\,NH.CO.NH.SO_2}$$

and the other in which attempts were made to close the ring by treating the primary and secondary amides with phosgene,

$$:C(SO_2NHR)_2 + Cl.CO.Cl \longrightarrow :C\underline{.SO_2.NR.CO.NR.SO_2}$$

Method 1—Twelve Gm. of anhydrous aluminum chloride, 2 Gm. of dried urea and 7.1 Gm. of methylenedisulfonylchloride in 25 cc. of anhydrous carbontetrachloride were refluxed until the calculated amount of hydrogen chloride has been given off. None of the desired ureide could be obtained from the reaction mixture and the original methylenedisulfonylchloride was recovered quantitatively as the barium salt $CH_2(SO_3)_2Ba.H_2O$, and identified by analysis.

Method 2—Method 1 was repeated substituting carbondisulfide for the carbontetrachloride but again none of the desired ureide was obtained and the methylenedisulfonylchloride was recovered quantitatively as the barium salt and identified by analysis.

Method 3—When the disulfonylchloride was heated with urea in the absence of a solvent or a condensing agent it formed a thick homogeneous mixture with the evolution of a gas and heat, but none of the desired ureide could be isolated and the original methylenedisulfonylchloride was recovered and identified as the barium salt.

Methods 4, 5, 6—Similar experiments were carried out using no condensing agent and using sodium ethoxide and sodium bicarbonate as condensing agents, but in each case none of the desired ureide was obtained and the original methylenedisulfonylchloride was recovered quantitatively as the barium salt and identified by analysis.

Method 7—0.01 mol. (3.3 Gm.) of methylenedisulfonanilide were bombed for seven hours at 100° C. with 7 cc. of a benzene solution containing 0.01 mol. of phosgene. None of the expected ureide was obtained and 3 Gm. of the original anilide were recovered and identified by the mixed melting point method.

Method 8—0.01 mol. of phosgene was permitted to react with 0.01 mol. of methylenedisulfonanilide in the presence of 0.02 mol. of pyridine in benzene solution, and although all of the original anilide could not be recovered, none of the expected ureide was obtained.

Method 9—0.01 mol. of N,N′-dipotassium methylenedisulfonanilide was bombed for six hours at 120° to 130° C. with 0.01 mol. of phosgene in benzene solution. Much decomposition occurred and only about one-half of the original anilide could be recovered from the reaction mixture. A few crystals of a sulfur containing organic compound were also obtained which, after washing with alcohol, melted with decomposition between 277° and 281° C. These crystals could not be identified as the cyclic ureide.

Preparation of N,N′-Dipotassium Methylenedisulfonanilide.—Four hundredths mol. (12.8 Gm.) of the anilide were refluxed for three hours with an excess of alcoholic potassium hydroxide. The cooled reaction mixture was filtered and 13.5 Gm. of the white crystalline dipotassium derivative were obtained. The product was purified by crystallization from hot dilute alcohol and identified by analysis.

	Wt. of Sample.	Wt. of $BaSO_4$.	Per Cent of Sulfur.
Calculated for $H_2C(SO_2NKC_6H_5)_2$	0.1507 Gm.	0.1748 Gm.	15.94
Observed	0.1507 Gm.	0.1762 Gm.	16.05

DISCUSSION.

Methylenedisulfonic acid and malonic acid are not only similar in structure but they also have many properties in common. The analogy between the activity

of the methylene hydrogen atoms of these two compounds is extremely interesting and suggests the possibility of the synthesis of a series of derivatives exactly analogous to the barbiturates. Unfortunately this is not entirely possible. Alkylation of the arylesters and arylamides can be effected in a manner similar to the malonic acid synthesis, but certain differences in the properties of these two compounds defeat efforts to prepare methylenedisulfonic acid derivatives simulating the barbiturates. The alkylesters of methylenedisulfonic acid do not permit efficient alkylation and when treated with alcohol or ammonia they exhibit properties characteristic of the alkylesters of sulfuric acid. It might be stated that this similarity to sulfuric acid should be expected since the alkylmonosulfonic acids possess some of these properties. However, the insolubility of barium methylenedisulfonate and the inability to form alkylesters and amides from methylenedisulfonylchloride are certainly exceptions to the recognized properties of the alkylmonosulfonic acids.

In spite of our many unsuccessful attempts to prepare cyclic ureides of methylenedisulfonic acid we still are not convinced that these compounds cannot be made. It is our opinion that the properties of the dialkyl derivatives of the free acid might approach those of the more characteristic organic compound malonic acid, and permit the preparation of the cyclic ureide. It was this opinion that encouraged us to endeavor to prepare the free dialkylmethylenedisulfonic acids.

SUMMARY.

1. Methylenedisulfonic acid and a number of its derivatives have been prepared and studied.

2. Methods of hydrolyzing dialkylmethylenedisulfonic acid arylesters and amides have been studied.

3. A number of attempts to prepare the cyclic ureide of methylenedisulfonic acid have been made under varying conditions.

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ACORNS OF QUERCUS RUBRA.*

BY C. J. MONARCA AND E. V. LYNN.[1]

Remarkably little attention has been paid to the chemical composition of the common acorn, although it can be obtained in almost unlimited quantity. Attempts have been made repeatedly to utilize the kernels as fodder for cattle, swine and poultry but, because of the tannin content, they are apparently disagreeable

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[1] Massachusetts College of Pharmacy, Boston, Mass., June 20, 1936.

to the animals even after supplementary mixture with other foods. The fixed oil, however, might find some value in pharmacy and as an edible material. The few analyses which have been made on foreign species would certainly indicate that the product could so be used.

The fruits of the red oak seem to offer considerable possibility along this line. They are abundantly produced from trees which are very common in New England and undoubtedly could be collected in large quantities every year.

A lot of about 30 pounds of these was collected in the fall of 1935 from trees which were identified by Professor Youngken, of the Massachusetts College of Pharmacy. About 35 per cent was found to be shell and 65 per cent kernels. Partial analysis of the latter gave: moisture 11.02; protein (N × 6.25) 4.41; starch 28.23; tannin 11.74; ether extract 11.03 per cent. The high content of tannin and low protein probably explain the objections to using the kernels as a food for animals.

The oil was extracted from several pounds of the macerated material by means of ether, which was subsequently distilled off, the last portions being removed by careful æration. There was thus obtained nearly a liter of light brown product, depositing about 20 Gm. of solid matter which was not further examined. Analysis of the oil gave the following results:

Specific gravity at 25° C.	0.9141	Unsaponifiable residue	0.9
Refraction at 20° C.	1.4725	Iodine number	100.1
Solidifying point	6.2° C.	Hehner value	90.6
Titer test of acids	13.1° C.	Soluble acids	0.2
Saponification number	195.3	Maumene test	49° C.
Acid number	4.5	Reichert-Meissl value	1.1
Ester number	190.8	Polenske value	0.8
Acetyl value	5.3		

Using the common method involving solubility of the lead salts in ether, the liberated acids were separated roughly into a solid and a liquid portion. The isolated solid acids had a melting point of 53° C. and an iodine number of 6.04 and, correcting for the latter, amounted to 9.22 per cent. By exposing a saturated solution in ether to a temperature of −5° C., it was possible to obtain a portion melting at 56.2° C. and having an acid number of 284 and a second portion with 51° C. and 272, respectively. Apparently most of the solid acids consist of stearic acid with smaller amounts of palmitic.

The oil contained mostly liquid acids with an iodine number of 110.3, giving by calculation a total of 76 per cent. Bromination of the product gave rise to no substance insoluble in petroleum ether, acetone or chloroform and no separation could be obtained from the resulting solutions at low temperatures. One can conclude that the liquid acids consist chiefly of oleic and, because of the high iodine value, one of the linoleic acids. Linolenic acids, which give solid hexabromides, must be absent.

We find, therefore, that the fixed oil from acorns of *Quercus rubra* is somewhat similar to that from other species of oak. It is also clearly related to other oils of the semi-drying and non-drying classes, such as olive and cottonseed. The taste of the material is quite agreeable and there seems to be no doubt that it could be employed successfully as emollient in medicine and probably in other ways in which fats are generally applied. We are at present contemplating a more complete study of composition and of methods for collection and refining.

SUMMARY.

1. Analysis was made of the kernels of *Quercus rubra* and of the oil which they contain.

2. The oil consists largely of glycerides of oleic, linoleic, stearic and palmitic acids. It conforms closely to other fatty oils used in medicine.

THE BARK OIL OF DOUGLAS FIR.*

CARL H. JOHNSON[1] AND RUSSELL A. CAIN.[2]

The bark of the young Douglas fir, *Pseudotsuga taxifolia* (Poir.) Britt., is characterized by the presence of numerous resin blisters which disappear as the tree grows older while the bark becomes thicker and deeply furrowed. It was from this young bark that the oil used in this investigation was obtained.

EXPERIMENTAL.

Pieces of bark were cut from selected trees growing in the vicinity of Seattle, Washington, and subjected to steam distillation. From 64 pounds of fresh bark there was obtained a total of 338 cc. of oil which corresponded to a yield of 1.01 per cent. The oil was slightly greenish in color and possessed a very pleasing aromatic odor.

The physical constants of the oil were determined in the usual manner with the following results: d_{20} 0.8721; n_D^{20} 1.4750; $[\alpha]_D^{23}$ −24.25°; saponification number 11.9; acid number 0.71; ester number (calculated) 11.19; per cent of ester (calculated as geranyl acetate) 3.9; saponification number, after acetylization 62.4; per cent of total alcohol (calculated as geraniol) 17.5; per cent of free alcohol (calculated as geraniol) 14.4.

Free Acids.—Extraction of 250 cc. of the oil with a 5 per cent aqueous solution of sodium carbonate gave 0.2102 Gm. of a brown gummy residue which was slightly acid to litmus and possessed a faint odor. The residue was dissolved in ether and steam distilled, whereupon an aqueous distillate was obtained on the surface of which floated a small amount of insoluble material. Attempts were made to identify acids present in both the soluble and insoluble distillates but without success. The odor of the distillates as well as their reactions to litmus indicated at least the presence of traces of acids such as capric or caproic.

Phenols.—Extraction by 5 per cent aqueous solution of sodium hydroxide yielded 0.1767 Gm. of a resinous brown residue possessing a faint odor. The residue did not respond to any of the general tests for phenols, hence it was concluded that no phenols were present in the bark oil.

Fractionation.—The oil, which had been extracted with the sodium carbonate and sodium hydroxide solutions, was washed with water and dried. The 238 cc. of oil which remained were fractionated at 25-mm. pressure and that portion boiling up to 100° C. was separated. This lower boiling portion, which measured 184 cc. and represented 73.6 per cent of the original oil, was resolved into its various constituents by repeated refractionations. The fractions as finally obtained, together with their physical constants, are as follows:

Fraction No.	Boiling Point at 25 Mm.	Amount.	Sp. Gr. 20° C.	n_D^{20}.	$[\alpha]_D^{23}$.	Color.
I	65–71° C.	88 cc.	0.8575	1.4751	−35.21°	Colorless
II	71–80	75	0.8586	1.4804	−25.59	Colorless
III	80–100	21	0.8720	1.4866	−11.08	Colorless

Levo Alpha Pinene.—A portion of the first fraction was oxidized to pinonic acid with potassium permanganate according to the method of Tiemann and Semmler (1). The semicarbazone

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which was formed by treating the acid with semicarbazide hydrochloride melted, after purification at 203° to 204° C. No depression of the melting point was noted when mixed with the semicarbazone of known pinonic acid. The preparation of this derivative showed the presence of alpha pinene in the fraction.

Levo Beta Pinene.—A small amount of Fraction I was oxidized to nopinic acid according to Wallach's Method (2). After several recrystallizations from ether, the acid melted at 126° to 127° C. The preparation of the acid identified beta pinene.

Levo Camphene.—In addition to the alpha and beta pinenes, camphene was also identified as being present in the first fraction. A 30-cc. portion of the fraction was hydrated by the well-known Bertram and Walbaum method (3). After hydration there remained 24 cc. of non-reacting material which was discarded. The isoborneol which was obtained as a result of the saponification of the bornyl acetate was purified by recrystallization from petroleum benzene and melted at 203° C. The phenylurethane melted at 136° C. Based on the fact that 24 cc. of the fraction was discarded it was assumed that the fraction contained approximately 20 per cent camphene.

Fraction II contained traces of both alpha and beta pinene.

Dipentene.—A portion of the third fraction was diluted with ether and the well-cooled mixture saturated with HCl gas. As a result the crystalline dihydrochloride was obtained, which after purification melted at 50° C. When mixed with the dihydrochloride of pure *d*-limonene the melting point was found to be 49° C. Since limonene dihydrochloride depresses considerably the identical melting point of terpinene dihydrochloride but not that of the dipentene compound, it was concluded that this fraction contained limonene or dipentene but not terpinene. To differentiate between the two former compounds the tetrabromide was prepared, according to the method of Wallach (4). Repeated recrystallization from ethyl acetate failed to raise the melting point above 118° C., although a melting point of 123° to 124° C. is given in the literature for dipentene tetrabromide. Although the melting point of 118° C. would indicate the presence of traces of limonene it was concluded that dipentene was the chief constituent of the fraction.

Saponification of the Higher Boiling Portion.—The higher boiling oil was saponified by heating with alcoholic potassium hydroxide and then submitted to several refractionations at 25-mm. pressure.

Fraction No.	Boiling Point at 25 Mm.	Amount.	Sp. Gr. 20° C.	n_D^{20}.	$[\alpha]_D^{26}$.	Color.
I	105–125° C.	14 cc.	0.8910	1.4877	−11.6°	Yellowish
II	125–150	2	....	1.4878	− 6.0	Yellowish
III	150–190	2.5	0.8820	1.5075	0.0	Greenish
IV	150 and above	2	....	....	....	Black

Geraniol.—Both Fractions I and II were dissolved in pyridine and treated with diphenylcarbamine chloride according to the method of Erdmann and Huth (5), with the result that in each case geraniol diphenylurethane was obtained. The crystalline derivative after several recrystallizations from hot alcohol melted at 82° C. Due to the large amount of this derivative formed it was concluded that both fractions consisted almost entirely of geraniol.

Azulenogenic Sesquiterpenes.—The presence of azulenogenic sesquiterpenes in the third high boiling fraction was indicated by treatment according to S. & H. Sabetay's method (6). Due to the small amount of fraction no further attempts at identification were made.

Fraction IV which consisted of a brown tarry residue showed signs of partial decomposition and no analysis was made.

Combined Acids: Acetic Acid.—The alkaline solution obtained from the saponification of the oil was evaporated to dryness, and the residue was made acid and distilled. A very small amount of insoluble distillate was obtained from which it was impossible to prepare satisfactory silver salts. The aqueous portion of the distillate when made alkaline and evaporated to dryness gave the general qualitative tests for acetic acid. The combined acids, therefore, consisted of acetic acid together with possible traces of acids of higher molecular weight, as indicated by the odor.

SUMMARY.

The bark from the young trees yielded 1.01 per cent of volatile oil consisting of approximately 75 per cent of terpenes and 16 per cent of higher boiling con-

stituents including an alcohol and probably sesquiterpenes. The oil contained about: 28 per cent levo alpha pinene; 24 per cent levo beta pinene; 7 per cent levo camphene; 8 per cent dipentene; 6 per cent geraniol partly as the acetate; a small amount of azulenogenic sesquiterpene. Traces of free acids were present, probably capric or caproic, while acetic acid was present in the combined state.

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THE EFFECT OF CYSTINE ON THE TOXICITY AND TRYPANOCIDAL ACTIVITY OF NEOARSPHENAMINE.*

BY A. E. JURIST AND W. G. CHRISTIANSEN.[1]

It is well known that neoarsphenamine injected intravenously in aqueous solution at times causes undesirable reactions of varied nature and severity. Consequently many attempts have been made to find some substance or substances which could be used either simultaneously with neoarsphenamine or during the course of the treatment to reduce both the frequency and severity of these reactions or eliminate them altogether. Particular attention has been paid to sulfur compounds owing to the effectiveness of sodium thiosulfate in arsenic poisoning reported first by Ravaut (1) and then by McBride and Dennie (2). Subsequently Raiziss (3), Groehl and Myers (4) and many others have pointed out that sodium thiosulfate might have a favorable effect in preventing neoarsphenamine reactions when given at the same time as the arsenical. At the present time, however, sodium thiosulfate is used in arsphenamine therapy, mainly for the treatment of the more severe occasional reactions such as dermatitis, jaundice; it hastens elimination of the arsenic.

More recently Sullivan (5) has pointed out that cystine is one of the amino acids most necessary to normal body growth and maintenance and plays an important rôle in nutrition. It has also been reported by Sullivan in a private communication that colloidal sulfur therapy in arthritis raised the cystine content of the nails from the subnormal level of 8.67% to 10.78%, a close approach to the normal value of 12%. Also cystine is a known constituent of the hair. Further, it has often been reported that in instances of arsenical poisoning arsenic has been found in the skin, hair and nails. It appeared possible, then, on the basis of a consideration of the chemistry of cystine in relation to the chemical reactions of arsphenamines in the body, to convert the excess arsenic present in the skin before

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* Scientific Section, A. PH. A., Dallas meeting, 1936.

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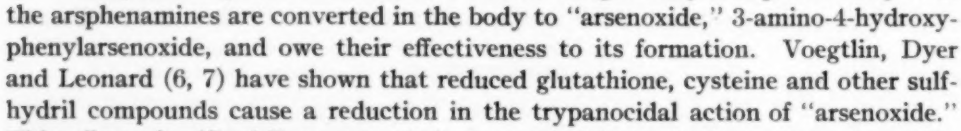
the onset of an arsenical dermatitis to a stable, less toxic form if the cystine or cysteine content of the epidermis could be raised to a sufficient level, thus averting the dermatitis.

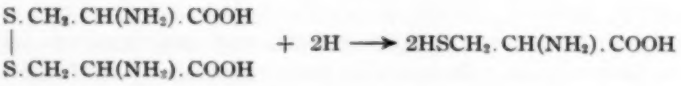
This possibility has its chemical basis in the generally accepted theory that the arsphenamines are converted in the body to "arsenoxide," 3-amino-4-hydroxyphenylarsenoxide, and owe their effectiveness to its formation. Voegtlin, Dyer and Leonard (6, 7) have shown that reduced glutathione, cysteine and other sulfhydril compounds cause a reduction in the trypanocidal action of "arsenoxide." This effect of sulfhydril compounds is due probably to the formation of a stable arsenical of the following type:



Arsenicals of the latter type have been prepared by Kharasch (8). They are more stable than arsphenamines and have been shown by Cohen, King and Strangeways (9, 10) to have a lower trypanocidal activity, in agreement with the observations of Voegtlin, et al. Also, they are clinically less effective as shown by the work of Becker and Obermayer (11), Connor, Shaw, Levin and Palmer (12), and Robinson and Moore (13) in their work on "Thioarsene," a compound of the above type obtained from 4-acetamidophenylarsenoxide and 4-mercaptobenzenesulfonic acid, and known chemically as disodium bis-(*p*-sulfophenyl)(acetamidophenyl)-dithioarsenite.

On the basis of the foregoing considerations it is not unreasonable to hope that if the arsenic present in the epidermis during arsphenamine therapy exists in the form of the "arsenoxide" it may be possible, by elevating the cysteine content of the epidermis, to so bind the arsenic in the form of such stable compounds as are described above as to render it less toxic and thus prevent the development of arsenical dermatitis. Therefore, it was decided to investigate this question. Before undertaking experimental work, however, it was necessary to select the sulfur compound to be used for this purpose.

The choice lay between cysteine and cystine because it was believed that if any effect at all was obtained it might be accomplished most efficiently with either cysteine itself or with cystine from which cysteine is obtained by reduction; *viz.*,



In view of the fact that cysteine is itself a sulfhydril compound and might directly reduce the effectiveness of an arsphenamine as shown by Voegtlin, Dyer and Leonard (*loc. cit.*), and in view of the fact that cysteine is less stable than cystine it was decided to utilize the latter in our experiments in conjunction with neoarsphenamine. It was believed that cystine would serve as a source of cysteine which could then react in the manner shown above.

Further, it is known that arsphenamines which are powerful reducing agents, will reduce cystine to cysteine. It was therefore thought undesirable to administer the cystine and neoarsphenamine simultaneously because the formation of cysteine by reduction of the cystine and the resultant oxidation of the neoarsphen-

amine to the corresponding arsenoxide derivative would permit the formation of a more stable, less effective dithioarsenite of the type discussed above. Since any possible reduction in the effectiveness of the arsenical was undesirable an attempt was made to avoid such a circumstance by administering the cystine orally on the day following the injection of the neoarsphenamine.

Our experiments showed that the toxicity of neoarsphenamine was not materially altered when one Gm. of cystine per Kg. of body weight was administered orally on the day following the injection of 350 mg./Kg. of neoarsphenamine in albino rats. On the other hand when doses of 250 mg. and 500 mg. of cystine per Kg. of body weight were administered orally on the day following the injection of from 5.0 mg. to 9.0 mg. of neoarsphenamine per Kg. of body weight in albino rats infected with *T. equiperdum*, the trypanocidal action of the arsenical was noticeably reduced. These results indicate that it is not advisable to administer cystine during the treatment of syphilis with neoarsphenamine and that in spite of planning the method of treatment so as to avoid any reduction in the activity of the arsenical this result was not accomplished.

If cystine reduces the effectiveness of neoarsphenamine by serving as a source of cysteine in the body and if the cysteine in turn combines with the arsenical in the manner described herein, then any sulfur compound which will raise the cystine content of the body will cause a reduction in the trypanocidal activity of neoarsphenamine. It is probable that the mechanism by which it was hoped to reduce the possibility of arsenical dermatitis with cysteine originating from the administration of cystine, namely, the formation of a dithioarsenite from cysteine and arsenoxide, is the one by which cystine reduced the trypanocidal activity of neoarsphenamine. However, in this case cystine, or more probably cysteine formed by its reduction in the body, reacts to form a stable, less trypanocidally effective dithioarsenite with the arsenoxide formed by oxidation of the neoarsphenamine in the blood stream, liver and other parts of the body of the infected animals used in these experiments.

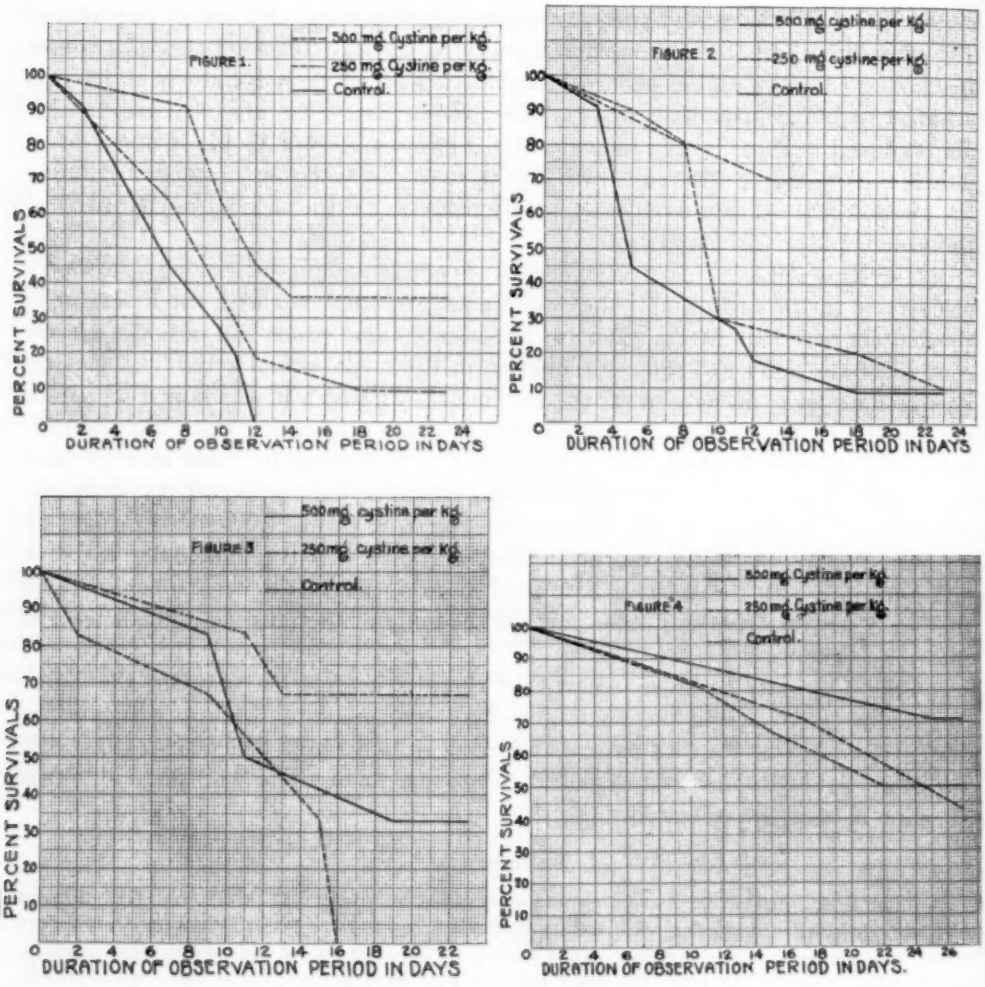
This does not, however, mean that there is no relation between the sulfur content of the skin and the possibility that arsphenamine therapy will produce dermatitis. It may be that patients suffering from a sulfur deficiency of the skin are more liable to have an arsenical dermatitis than those who do not. This question is being investigated.

EXPERIMENTAL.

The toxicity of neoarsphenamine was determined on albino rats at 350 mg./Kg. Eleven rats were injected on one day with neoarsphenamine and on the next day, twenty-four hours after the injection, a dose of cystine equivalent to one Gm. per Kg. of body weight was administered orally to five of the rats; the other six were kept as controls. There were two deaths in the five animals which received both neoarsphenamine and cystine and two deaths in the six animals which received neoarsphenamine but no cystine. There was no material difference in the gross appearance of the kidneys of the surviving animals when they were killed at the end of the test period, irrespective of whether they had received cystine or not. The results show no material change in the toxicity of the neoarsphenamine due to the administration of cystine.

The effect of cystine on the trypanocidal action of neoarsphenamine was determined on albino rats infected with *T. equiperdum* using three different doses of neoarsphenamine, namely, 5.0 mg., 7.5 mg. and 9.0 mg. per Kg. of body weight and at each of these dosages the effect of both 250-mg. and 500-mg. doses of cystine was determined. In all instances two doses of neo-

arsphenamine were given intravenously and each was followed on the next day by a dose of cystine orally; the time between doses of neoarsphenamine varied from two to six days. At each neoarsphenamine dose level experiments were carried out with controls receiving no cystine. The trypanosome count just prior to the neoarsphenamine injection varied from 18,000 to 260,000 per cu. mm. of blood. In these experiments groups of six to eleven animals were used for each dose level of neoarsphenamine and cystine, making a total of 102 animals in all. All animals were observed for twenty-one days after the last injection unless death ensued in the meantime. The results obtained are given in the following series of curves:



Figures 1 and 2 give two sets of results obtained with two 5.0 mg. per Kg. doses of neoarsphenamine two days apart.

Figure 3 gives the results obtained with two 7.5 mg. per Kg. doses of neoarsphenamine two days apart.

Figure 4 gives the results obtained with two 9.0 mg. per Kg. doses of neoarsphenamine six days apart.

At the 5.0 mg. per Kg. dose of neoarsphenamine as in Figs. 1 and 2 the results show a lower percentage of survival for the infected animals receiving 500 mg. per Kg. of cystine than for those

which received 250 mg. per Kg. of cystine, while the controls show a still higher percentage of survival at the end of the twenty-three day period of observation. With 7.5 mg. per Kg. of neoarsphenamine the results from the two cystine experiments are anomalous but here again the controls show a definitely higher percentage of survival at the end of the observation period. At the 9.0 mg. per Kg. dose the percentage of survivals is not very different for animals receiving 250 mg. per Kg. of cystine and the controls are somewhat higher for those receiving 500 mg. per Kg. of cystine. However, since the 9.0 mg. per Kg. dose of neoarsphenamine is almost the Minimal Sterilizing Dose in rats infected with *T. equiperdum* it would be expected that the effect of cystine would be less noticeable. Further, the number of animals tested at this dosage was smaller than at 5.0 mg. and 7.5 mg. per Kg. greatly increasing the possibility of error.

The results show clearly that the trypanocidal effectiveness of neoarsphenamine is materially reduced by the administration of cystine during the period of neoarsphenamine therapy.

We gratefully acknowledge the assistance of the Biological Laboratories of E. R. Squibb & Sons in conducting the biological tests reported herein.

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THE CHEMICAL NATURE OF IODOBISMUTHIC ACID AND ITS RELATION TO THE CHEMISTRY OF THE ALKALI IODIDE. COMPOUNDS OF BISMUTH IODIDE.*

BY A. E. JURIST AND W. G. CHRISTIANSEN.[1]

Recently Motard (1), François (2), Delwaulle (3) and François and Delwaulle (4) have identified a number of alkali metal iodide compounds of bismuth iodide and antimony iodide. While studying the chemistry of Iodobismitol, which is a solution of sodium iodobismuthite and sodium iodide in a glycol, preferably propylene glycol, the structural characteristics of the compound sodium iodobismuthite have been investigated. A compound which might be an iodobismuthic acid, having the formula BiI_3, HI, $3\,H_2O$, has already been isolated by Arppe (5) but no relation between it and the alkali metal iodide-bismuth iodide compounds has yet been shown.

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* Scientific Section, A. PH. A., Dallas meeting, 1936.

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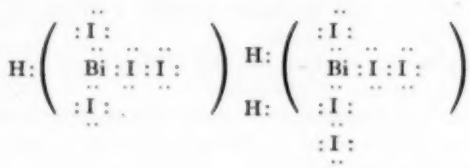
Noyes, Hall and Beattie (6) studied the solubility of bismuth oxychloride in hydrochloric acid and thereby reached the conclusion that there were probably chlorobismuthic acids having the formulas $HBiCl_4$ and H_2BiCl_5. Similarly, by studying the solubility of bismuth oxyiodide in hydriodic acid, applying the method of Noyes, Hall and Beattie, we have determined that there are two iodobismuthic acids of the formula $HBiI_4$ and H_2BiI_5 analogous to the two chlorobismuthic acids described above. It is not unlikely that the corresponding chloro- and iodo-antimonic acids could be demonstrated.

If the results of this work are combined with the demonstrated fact that bismuth is in the anion in sodium iodobismuthite (7) it is quite probable that sodium iodobismuthite as used in Iodobismitol is a salt of the iodobismuthic acid H_2BiI_5. Similarly it is probable that all the alkali metal iodide compounds of bismuth and antimony iodides described by François and Delwaulle (*loc. cit.*) represent alkali metal salts of iodobismuthic acids or iodoantimonic acids. If we consider the structure of the two iodobismuthic acids in the light of modern theories the following arrangements appear possible for $HBiI_4$ and H_2BiI_5.



In these two acids bismuth iodide remains unaltered. In the acid $HBiI_4$ it, together with the iodide ion from one molecule of hydriodic acid, yields the complex anion, BiI_4; the hydrogen atom from the hydriodic acid is attached to this entire anion—the latter has one free electron which is set free when the two iodine atoms become attached as indicated above. Similarly in the acid H_2BiI_5 two iodine atoms from two molecules of hydriodic acid together with the molecule of bismuth iodide, yield the anion BiI_5, and two electrons are set free so that this acid has two ionizable hydrogen atoms, instead of one, as in $HBiI_4$. In both cases the electronic character of the bismuth is unchanged from that in bismuth iodide. A distinction is being made between the electrical character of the bismuth atom and the character of the group containing it.

These two structures would then readily account for the existence of salts in which alkali metals occupy the positions indicated above for hydrogen atoms. In the salts such as the sodium iodobismuthites the bismuth is, as in the case of the acids, part of an anion which is electronegative in character. The presence of the bismuth in the complex anion such as shown here accounts for the fact that bismuth in Iodobismitol upon electrolysis migrates as a part of the anion without itself being electronegative.

EXPERIMENTAL.

The method used was to place two Gm. of bismuth oxyiodide in an ampul with 10 cc. of hydriodic acid, varying the concentration of the latter with each experiment. The ampuls were sealed and rotated in a constant temperature bath for 72 hours or longer at 25° C. The ampuls were then opened and specific gravity, iodine and bismuth determinations were made on the clear supernatant layer. The solid phase was also assayed for its bismuth and iodine content in order

to determine whether any changes in its composition had taken place. These assays showed that the solid phase changed gradually from bismuth oxyiodide to bismuth iodide with increasing acid concentrations and that the major portion of the solid phase was bismuth iodide in all experiments in which the bismuth concentration in solution became considerable.

The method of calculating the mass action constants at the different acid concentrations follows that of Noyes, Hall and Beattie (6). Briefly, it is as follows. The reaction between the bismuth oxyiodide and hydriodic acid is expressed by the following three equations.

$$BiOI + 2HI = BiI_3 + H_2O \quad (1)$$
$$BiOI + 3HI = HBiI_4 + H_2O \quad (2)$$
$$BiOI + 4HI = H_2BiI_5 + H_2O \quad (3)$$

In order to set up from these equations the formulas representing the mass-action constants it is necessary to assume that $HBiI_4$ and H_2BiI_5 have the same degree of ionization as hydriodic acid. The concentration of hydrogen ion is calculated by subtracting three times the bismuth concentration from the iodine concentration since the concentration of hydrogen ion from hydriodic acid must equal the iodide ion from the same source while the concentration of iodide ion from hydriodic acid must equal the total iodine content minus that present as bismuth iodide (BiI_3). The actual hydrogen ion is then calculated by multiplying the latter difference by the degree of ionization of hydriodic acid at the concentration determined. The three mass-action equations corresponding to (1), (2) and (3) are respectively:

$$\frac{\Sigma Bi}{(\Sigma H)^4\gamma^4} = K \quad (4)$$

$$\frac{\Sigma Bi}{(\Sigma H)^3(\Sigma H - \Sigma Bi)^3\gamma^4} = K_1 \quad (5)$$

$$\frac{\Sigma Bi}{(\Sigma H)^3(\Sigma H - 2\Sigma Bi)^4\gamma^4} = K_2 \quad (6)$$

In these equations ΣBi and ΣH represent the total dissolved bismuth and total hydrogen-ion concentrations in atomic weights per 1000 Gm. of water and the term γ represents the degree of ionization of hydriodic acid at the hydrogen-ion concentration existing in the experiment. The calculation of the mass-action constants K, K_1 and K_2 would have been more accurate had the activity coefficient for hydriodic acid been available, substituting it in these equations for the degree of ionization. The degree of ionization of hydriodic acid was calculated for the different concentrations from the conductivity data for hydriodic acid given in "International Critical Tables," Volume 6.

The data obtained in these solubility studies and the constants calculated from them are given in the following table. All concentrations are expressed in terms of atomic weights per 1000 Gm. of water.

TABLE I.

Experiment Number.	Density of Solution at 25° C.	Iodine Concentration.	Bismuth Concentration ΣBi.	Hydrogen Concentration ΣH.	Degree of Ionization of $HI\gamma$.	K.	K_1.	K_2.
1	0.9952	0.1802	0.0260	0.1022	0.930	318.6	7521.4	563470.0
2	0.9934	0.1847	0.0189	0.1280	0.920	98.23	1240.0	22920.0
3	0.9953	0.1528	0.0076	0.1300	0.920	37.14	342.3	3928.5
4	0.9955	0.1877	0.0170	0.1367	0.920	69.54	740.4	12407.0
5	1.0349	0.4971	0.0546	0.3333	0.885	7.212	37.01	359.0
6	1.0955	0.9809	0.1624	0.4937	0.868	4.816	21.11	1661.7
7	1.1731	1.5945	0.2886	0.7287	0.837	2.085	12.99	2511.4
8	1.1924	1.8206	0.3286	0.8348	0.820	1.497	8.041	1278.5
9	1.2451	2.3571	0.4590	0.9801	0.810	1.155	7.844	92142.0
10	1.3070	2.7756	0.5489	1.1289	0.788	0.877	5.725	1515300.0

All concentrations are given in terms of atomic weights per 100 Gm. of water.

The foregoing data show that an equilibrium exists between two acids of the formula $HBiI_4$ and H_2BiI_5. When the results obtained for K, K_1 and K_2 as given in the foregoing table are plotted using the logarithms of K, K_1 and K_2 against ΣH, the hydrogen concentration, this will become apparent. These curves show that the reaction between bismuth oxyiodide and hydriodic acid is neither a fourth order reaction nor a fifth order reaction but an equilibrium between the two.

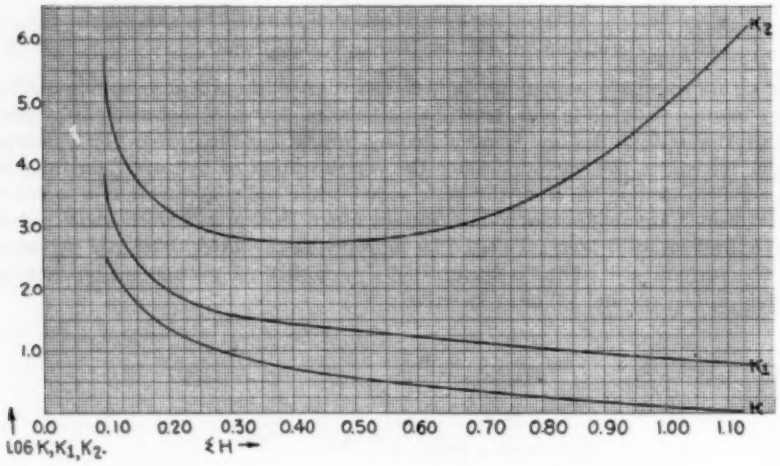


Fig. 1.

This means, then, that iodobismuthic acid is a mixture of two acids $HBiI_4$ and H_2BiI_5. Therefore salts of both acids can exist.

SUMMARY.

By studying the solubility of bismuth oxyiodide in hydriodic acid the existence of two iodobismuthic acids, $HBiI_4$ and H_2BiI_5, has been demonstrated. This indicates that the sodium iodobismuthites are salts of these acids. The bismuth in these salts is anionic in that the bismuth iodide molecule has become part of a complex anion.

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(2) François, *Ibid.*, 198, 1994 (1934); 200, 393 (1935); 201, 215, 1489 (1935).
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(4) François and Delwaulle, *Bull. soc. chim. Mém.* (5), 3, 687 (1936).
(5) Arppe, *Akad. Handl. Stockholm*, 133 (1842).
(6) Noyes, Hall and Beattie, *J. Am. Chem. Soc.*, 39, 2526 (1917).
(7) Jurist and Christiansen, A. PH. A., 23, 15 (1934).

OUR RESPONSIBILITIES.

As one looks around we are concerned with the status of personal character, the disregard of responsibility. Education is essential for all, but personal character shapes the results of education. No age nor time has been free from selfish motives nor individual yield to self-gratification.

Perfection cannot be credited to any one group nor all imperfections charged to the other—that is secondary to coöperation for results.

STUDIES UPON PRECIPITATION IN FLUIDEXTRACT OF SENNA. III.*

The Prevention of Precipitation in Fluidextract of Senna by the Addition of Borax and Other Agents.[1]

BY KARL L. KAUFMAN[2] AND C. O. LEE.[3]

In a previous paper it was noted that borax, when added to fluidextract of senna, markedly reduced the amount of precipitate. Accordingly, numerous samples of the preparation were prepared and treated with borax for study. It was our purpose to determine the optimum concentration of borax necessary to yield a minimum of the precipitate in the fluidextract. To this end two series of six samples each of the fluidextract were prepared. One sample of each series served as the control. To the other samples varying amounts of borax were added. After 48 hours all samples were filtered and set aside for later observations. The details are recorded in Table VI following.

TABLE VI.

Sample Number.	Gm. of Borax Added.	Precipitation after 128 Days.	322 Days.
71-A	None	++	+++
71-B	2.5	+	+
71-C	4.0	++	+++
71-D	5.0	++	+++
71-E	7.5	++	++++
71-F	None[1]	+	++
		87 Days.	120 Days.
191-a	None	+++	+++
191-b	1.25 (1/2%)	++	+++
191-c	2.50 (1%)	++	++
191-d	3.75 (1 1/2%)	+	+ to ++
191-e	5.00 (2%)	++	++
191-f	6.25 (2 1/2%)	++	++

[1] Adjusted to p_H 6.54 by the addition of NaOH and HCl solutions.

From the results of this experiment it was concluded that borax, as an agent for reducing precipitation in fluidextract of senna, was most effective in concentrations of 1.5 to 2.5 per cent. Furthermore, it seemed quite as effective, in this respect, after a period of 48 hours, as it did after 30 days.

THE EFFECTIVENESS OF BORAX IN RELATION TO TOTAL SOLIDS IN THE FLUIDEXTRACT.

Samples of fluidextract of senna, containing borax in concentrations of 2%, occasionally had somewhat more than a plus (+) deposit. It was thought that this variation in quantity of precipitate might be due to the differences in total solids in the samples of the fluidextract.

* Scientific Section, A. PH. A., Dallas meeting, 1936, see page 412, May JOURNAL, 1937.

[1] Based upon a thesis submitted to the Faculty of Purdue University by Karl L. Kaufman, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] J. K. Lilly Fellow, Purdue University, School of Pharmacy, 1933–1936.

[3] Professor of Pharmacy, School of Pharmacy, Purdue University.

To determine this, portions of a sample of a fluidextract, having a density of 1.067 and containing 22.4% W/W of solids, were increasingly diluted with the official menstruum. To each sample, except the control, there was added 2% W/V of borax. The samples were all filtered after 48 hours and set aside for observation. The results are given in Table VII, following.

TABLE VII.

Sample Number.	Cubic Centimeters. Sample.	Menstruum Added.	Gm. of Borax Added.	Precipitation after 77 Days.	126 Days.
181-1	250	None	None	++	+++
181-2	250	None	5	+	+
181-3	225	25	5	++	++
181-4	200	50	5	++	+++
181-5	175	75	5	+	+
181-6	150	100	5	++	++
181-7	125	125	5	++	++

No definite relationship could be noted between the total solids and the effectiveness of borax.

THE USE OF BORAX BUFFERS IN THE MENSTRUUM FOR FLUIDEXTRACT OF SENNA.

The effectiveness of borax as an agent in reducing precipitation in fluidextract of senna, when added directly to the preparation, has been shown. Efforts were next made to test its value when added to the menstruum rather than to the finished product.

Buffers were made up, consisting of borax-succinic acid, and borax-phosphate combinations according to Kolthoff (2). They ranged from p_H 4.0 to 8.4, inclusive, at intervals of 0.4 p_H. They were added in quantities equivalent to 10% of the menstruum.

Forty-three samples were prepared and studied over a considerable period of time. It was concluded that the borax-phosphate buffers, in the range p_H 6.4 to 8.4, were somewhat effective in reducing precipitation in fluidextract of senna.

BORAX AND OTHER BASIC SALTS.

The alkalinity of borax suggests itself as the mechanism by which the salt acts in reducing sedimentation in fluidextract of senna. If the answer is not in the alkalinity, but in the ions furnished by the borax, it then becomes a problem to determine the effective ion.

TABLE VIII.

Sample Number.	Reagent Added.	Precipitation after 116 Days.	172 Days.
151-2	2% $Na_2B_4O_7.10H_2O$	++	++
151-3	2% NaCN	+++++	++++
151-4	2% Na_2HPO_4	++++	++++
151-5	Control	++++	++++
		After 76 Days.	112 Days.
221-1	Control	+++	+++
221-2	2% CH_3COONa	++	+++

To test out these conjectures, six samples of fluidextract of senna were prepared. Two served as controls. To each of the other four were added basic salts having

an ion in common with that of borax, and a similar degree of alkalinity. All samples were filtered after 48 hours and set aside for observation. The details and results are summarized in Table VIII.

It appears that the sodium ion cannot be more than partly responsible for the reduced amount of precipitation following treatment with borax. Many similar experiments had previously been performed using small amounts of 10% sodium hydroxide solution, but the results were too erratic to be of value. In view of the known affinity of borax for complex formation, according to Dimroth and Faust (1), it would seem more likely that the borate ion was responsible. However, time did not permit us to extend these experiments sufficiently to prove the point. This is suggested as a topic for further study.

SUMMARY.

(*a*) It has been shown that treatment of fluidextract of senna with 2.0% borax and filtration after 48 hours markedly reduces precipitation in this preparation.

(*b*) There is apparently no direct relationship between total solids in the fluidextract of senna and the effectiveness of the borax.

(*c*) It was indicated that borate-KH_2PO_4 buffers might be helpful in reducing precipitation, when combined with the menstruum, replacing 10% of the water. The range of effectiveness was p_H 6.4 to 8.4.

(*d*) Evidence has been presented which indicates that the sodium ion of the borax can be only partly, if at all, responsible for reducing precipitation in fluidextract of senna.

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(2) Kolthoff, I. M., *J. Biol. Chem.*, 63, 135 (1925).

STUDIES UPON PRECIPITATION IN FLUIDEXTRACT OF SENNA. IV.*

THE NATURE AND PROPERTIES OF THE PRECIPITATE IN FLUIDEXTRACT OF SENNA.[1]

KARL L. KAUFMAN[2] AND C. O. LEE.[3]

The precipitate that commonly forms in fluidextract of senna is a dark brown, amorphous mass. It is lighter in color, and somewhat scaly when it forms in the cold.

A working quantity of the precipitate was obtained by making up a composite sample which was collected from many bottles of the fluidextract. These ranged in age from six months to three years. The precipitate was dried over calcium chloride and triturated to a fine powder. It was then subjected to various qualitative tests.

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* Scientific Section, A. PH. A., Dallas meeting, 1936.

[1] Based upon a thesis submitted to the Faculty of Purdue University by Karl L. Kaufman, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] J. K. Lilly Fellow, Purdue University, School of Pharmacy, 1933–1936.

[3] Professor of Pharmacy, Purdue University, School of Pharmacy.

SOLUBILITY.

Its solubility properties were studied according to the Dragendorff solvents. The averages of three such tests, expressed in per cent by weight, are as follows:

Petroleum ether	12.0%
Anhydrous ether	1.1%
Anhydrous alcohol	13.5%
Water	39.1%
0.15% NaOH solution	10.2%
0.10% HCl solution	15.1%
Total	91.0%

In addition to these, three other solvents were used and the solubility of the precipitate determined by weight differences. The results are as follows:

Water	50.0%
7% H_2SO_3 solution	5.8%
2% NaOH solution	12.3%

Numerous other liquids were tested for their solvent effects upon the precipitate, but none were of sufficient interest to report.

ASH ANALYSIS.

The ash content of the precipitate averaged 22.6% which is about twice the ash content of the crude drug.

Samples of the precipitate, collected from fluidextracts, 48 hours after being treated with borax, gave an ash yield of 33.48%. These samples contained some borax, which may account for the larger ash content.

INORGANIC QUALITATIVE ANALYSIS.

Four fractions of the precipitate were subjected to a qualitative analysis. The results are summarized in Table IX.

Those portions of the precipitate which remained insoluble in H_2SO_3 and NaOH solutions were a dirty, fluffy residue. Upon microscopic examination, tiny bits of plant materials were to be seen. The diatom *arachnoidiscus Ehrenbergii* was found to be a contaminant, although we are unable to explain its presence.

TABLE IX.

Ions Present.	Water-Soluble Portion.	Sulfurous Acid-Soluble Portion.	NaOH-Soluble Portion.	Water Extract of Ash from Residue.
Cations	Al, K,* Mg, Na	K*	Al, K,* Ca, Na	Ca, K*
Anions	SO_4, PO_4, Cl, NO_3, Si_2O_3	SO_4,* K_2SO_4 crystals	NO_3, SO_4, PO_4, CN, Si_2O_3	CO_3, Si_2O_3
Dialyzed portion	All of the above ions	.....	All of the above ions	.....
Dialysate	All of the above ions	.....	All of the above ions except silicate	.....

* Present in large amounts. The other ions listed were present in traces only.

CONSTITUENTS OF THE PRECIPITATE COMPARED WITH THOSE OF THE CRUDE DRUG.

As a procedure for examining the precipitate, the one given by Tutin (1) for the examination of the crude drug senna was used. In applying this technique

to the precipitate, certain minor adaptations were necessary, the details of which will not be discussed here. The presence of rhein, kaempferol, aloe-emodin and organic acids in the sediment of fluidextract of senna was indicated. These are also to be found in the crude drug.

A water-insoluble resinous substance was obtained from an alcoholic extract of the precipitate by subjecting the latter to steam distillation. In quantity it represented about one-sixth of the total solids extracted with alcohol.

About fifty per cent of this resinous substance was soluble in potassium hydroxide solution, the solution yielding a red color, characteristic of anthraquinone derivatives. According to its solubility in potassium hydroxide, this substance should consist of about one-half "acid resins," the remainder being "indifferent resin" or "resin anhydride." The alkali insoluble portion of this resinous mass was quite readily soluble in nitric acid.

THE PRECIPITATE FROM THE BORAX-TREATED SAMPLES OF THE FLUIDEXTRACT OF SENNA.

The precipitates from the borax-treated samples were subjected to solvent, and other tests. The results are summarized as follows:

1. The "borated" precipitates yielded about three per cent more alcohol-soluble extractive than the ordinary precipitates.

2. The "borated" precipitates yielded much more extraneous amorphous material than the regular precipitates. This made it hard to test for the constituents, but anthraquinone substances were in evidence.

3. Upon being subjected to steam distillation the "borated" precipitates were found to yield much less insoluble residue than the usual precipitates. The residue was not soluble in nitric acid and gave the hydroxyanthraquinone reaction.

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(2) Dragendorff, G., "Plant analysis," page 8, translated by H. G. Greenish.

NEW IODINE—BILE COMPOUND (IODOCHOLEATE).*

BY PAUL GOEDRICH.[1]

THE PHYSICAL AND CHEMICAL PROPERTIES, GERMICIDAL AND PHARMACOLOGIC ACTION.

At the time that iodine was introduced to medicine as a germ-killing agent its toxic properties were known, and they caused very much concern. This situation has not changed very much.

The destructive action of iodine to the broken and unbroken skin, especially when covered by cloths or bandages, limits its field largely to First Aid; also in preparing the operative field, iodine must be carefully removed by alcohol to avoid tissue necrosis.

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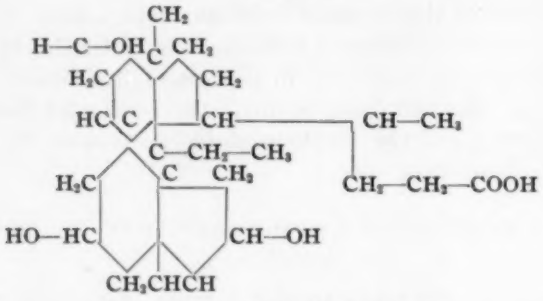
* Scientific Section, A. PH. A., Dallas meeting, 1936. Abstracted by the author for publication.

[1] From the Research Laboratories of the New Jersey College of Pharmacy, Rutgers University.

Iodine in the form of tincture and Lugol Solution is more than 100 years old, and all efforts to improve it have been limited.

In the course of experimentation on this subject, the author found a very surprising affinity of bile acids for iodine. In the natural bile these acids are present in the form of the sodium salt of the glycocholic and taurocholic acid, and so-called paired cholic acids.

CHART A.



Taurocholic Acid

$C_{20}C_{23}(CH—OH)_3—COOH—CH_2—SO_3H$

Cholic Acid — $CH—NH_2$

Amino-ethyl-sulfonic acid (Taurin)

Glycocholic Acid

$C_{20}H_{33}(CH—OH)_3—COOH—CH_2—COOH$

NH_2

Amino-acetic acid (Glycocol)

$(C_{26}H_{45}NSO_7)I_3$—Iodotaurocholic Acid

$(C_{26}H_{43}O_6N)I_3$—Iodoglycocholic Acid

It appears that these bile acids are compounds of the cholic acid with two different amino acids—the Glycocoll (Aminoacetic Acid) in case of the glycocholic acid, and the Taurin (Aminoethylsulphonic Acid) in the case of the taurocholic acid.

Until now it is believed that strong water solutions of iodine can only be made by addition of iodides. The choleates offer a new vehicle to obtain highly concentrated water solutions of iodine.

The bile salt, even in dry state, immediately forms a black iodine-like adsorption compound with the added iodine, which is soluble in water without any addition of iodides.

The question now arises whether the cholic acid alone would not also form a similar compound with iodine. This question is to be answered with yes and no. Cholic acid will form an adsorption compound with iodine, as was found a long time ago by Mylius and Kuester (1), but this compound is blue, unstable and not soluble in water, and it did not find any practical use. This indicates that the amino acid content of the natural bile acid has an important rôle in the formation of these compounds.

The complete adsorption takes place in proportion of one molecule of glycocholic acid to three atoms of iodine; if less glycocholic acid is used, free iodine appears in an ether extraction. The taurocholic acid forms the iodine compound in the same proportion. This, as far as our present knowledge goes, gives the iodoglycocholic acid the formula ($C_{26}H_{43}O_6N$) I_3 and the iodotaurocholic acid the formula ($C_{26}H_{45}NSO_7$) I_3. These compounds are soluble in water and also in alcohol, but not in ether, chloroform, carbon disulfide, etc. They give the blue starch reaction and are titrable with sodium thiosulphate.

CHART B.—IODINE ADSORPTION BY 5 CC. NORMAL HORSE SERUM.

Quantity of Used Iodine Solution.	Titrable Iodine Content.	Time of Exposure.	Starch-Iodine Reaction after Experiment.	Quantity of Iodine Recovered.
0.2 cc. U. S. P. Tincture	2.1%	5 min.	−	−
0.2 cc. Iodocholeate Solution	2.1%	5 min.	+	50%
0.5 cc. U. S. P. Tincture	2.1%	55 min.	−	−
0.5 cc. Iodocholeate Solution	2.1%	55 min.	+	50%
0.3 cc. U. S. P. Tincture	3.26%	10 min.	−	−
0.3 cc. Iodocholeate Solution	3.26%	10 min.	+	60%

An interesting feature of these compounds is that they combine much less with organic matter than tincture or Lugol's Solution, as Chart B indicates. The significance of this property will be seen in the bacteriologic and pharmacologic action. It might also be stated that steel and rubber are also very much less affected by the iodocholeates than by the tincture of Lugol's Solution. Among the physical properties of this product the most interesting one is the low volatility. It is well known that the tincture of iodine loses its iodine content rapidly after exposure, especially at body temperature and upon heating.

Iodocholeate solutions in water can be concentrated in open containers on the steaming water-bath, practically without any loss of Iodine.

CHART C.—CONCENTRATION TEST ON IODOCHOLEATE, TEMPERATURE 80° C.

Titrable Iodine Content before Concentration.	Original Quantity.	Concentrated to.	Iodine Content after Concentration.
1.48%	100 cc.	50 cc.	2.96%
2.1%	100 cc.	50 cc.	4.01%
3.02%	100 cc.	50 cc.	5.87%
4.1%	100 cc.	50 cc.	8.05%

To demonstrate the practical side of the low volatility, two series of tests were made. The first test was made by inserting for a short time a test-tube in a 7% U. S. P. tincture to a certain mark—and an identical test-tube in a 2% iodocholeate solution—then both test-tubes were dried for five minutes in the open air; after this time the remaining iodine was removed by alcohol and titrated.

The amount of retained iodine was the same in both experiments; in other words, a 2% iodocholeate solution was found to retain as much iodine as a 7% tincture.

CHART D.—IODINE RETENTION ON GLASS.

	Sample.	Iodine Content.	Time of Exposure.	Iodine Retention.
General average of 10 experiments	U. S. P. Tincture	7%	5 min.	Equal iodine retention.
	Iodocholeate solution	2%	5 min.	

IODINE RETENTION ON SKIN (FINGER).

	Sample.	Iodine Content.	Time of Exposure.	Iodine Retention.
General average of 10 experiments	U. S. P. Tincture	7%	10 min.	Equal iodine retention.
	Iodocholeate solution	2%	10 min.	

The penetration of iodocholeate solutions was tested by the Serum Agar Cup Method, using beef agar plus 10% blood serum as medium and *Staphylococcus aureus* as test organism; a solution of iodocholeate (1.25%) showed a clear zone of 13 mm. around the cup.

It is generally recognized that organic matter decreases the germicidal effect of all halogens. Undisputedly the bile salts are organic matter, therefore, it was to be expected that the germicidal power of the iodine in the iodocholeates would also be decreased. Contrary to these expectations it was found that the germicidal effect of the iodocholeates was considerably higher when compared with the Tincture or Lugol's Solution of the same content of titrable iodine.

In the course of years of experimentation with iodocholeates, the author and others have made hundreds of bacteriological tests of these compounds; they invariably have demonstrated the fact of the superior germicidal power of the iodocholeates.

The following chart will show the bacteriological effect of the iodocholeates compared with the tincture of iodine in varying concentrations at 20° C.

CHART E.—PHENOL COEFFICIENTS (F. D. A. METHOD).

Organism: *Staphylococcus aureus* at 20° C.

Material Used.	Phenol Coefficient.	Comparative Germicidal Potency.
Iodocholeate (6.033%)	9.2	Iodocholeate
Tr. Iodine (6.033%)	5.8	58.6% higher
Iodocholeate (4.030%)	7.1	Iodocholeate
Tr. Iodine (4.030%)	4.1	73% higher
Iodocholeate (3.114%)	5.5	Iodocholeate
Tr. Iodine (3.114%)	3.2	71.9% higher
Iodocholeate (2.264%)	4.5	Iodocholeate
Tr. Iodine (2.264%)	2.3	95.6% higher
Iodocholeate (1.878%)	3.7	Iodocholeate
Tr. Iodine (1.878%)	1.9	97.1% higher

Bactericidal Test Performed upon *Bacillus subtilis* (Spores).

Material.	5 Min.	10 Min.	15 Min.
U. S. P. Tr. of Iodine 7.15%	+	+	+
Iodocholeate-sol. 2.08%	−	−	−

(+) indicates growth.
(−) indicates no growth.
F. D. A. technique used. 4-Day old culture.

Phenol Coefficient Test in the Presence of 10% Sterile Serum.

Organism: *Staphylococcus aureus* at 20° C.

Material.	Phenol Coeffiicient.	Germicidal Potency.
Iodocholeate (2.264%)	$\frac{40}{60} = 0.66$	Iodocholeate 164% higher
Tr. Iodine (2.264%)	$\frac{15}{60} = 0.25$	

This demonstrates that the germicidal effect of the iodocholeate solution is up to 100% and more—higher than that of the tincture. The increase in germicidal effect is in reversed proportion to the iodine content of the iodocholeate solution when compared with tincture of the same content. The lowest concentration of iodocholeate shows the highest increase in germicidal effect against tincture of the same strength.

When 10% serum is added to the dilution the germicidal action is more than 2.5 *times* higher than the one of the tincture.

The F. D. A. Method for determination of phenol coefficient was used for this test. This method has its weaknesses and not too much weight can be given to the absolute figures, but since these tests have been made under absolute identical conditions the comparative value is correct. The chart also shows the germicidal effect on spore-bearing bacteria, which are the toughest organisms. A 7% tincture of iodine fails to kill the spores in 5, 10 or 15 minutes, whereas a 2% iodocholeate solution shows definite bacteriostatic action within five minutes.

The iodocholeates possess also a very good vermicidal action. This has been established by elimination of chicken worms from live chickens. About a 2.5% solution of iodocholeate was used, and the elimination of roundworms was 100%, apparently without any ill-by-effects to the birds.

In the pharmacologic action of the iodocholeates we find a considerable difference, when compared with the Tincture of Iodine or Lugol's Solution. The most important fact is, that the iodocholeate is not harmful to the broken skin, even when kept under heavy bandages.

We know that the Tincture or Lugol's Solution or other solutions of iodine, containing even less than 2% of iodine, will cause considerable tissue damage, necrosis, eventually gangrene, when kept under bandages for a prolonged time. The injury to the tissue is in direct proportion to the iodine content of the applied solution and the time of exposure. Iodocholeate, even in higher concentration, will not cause any irritation except redness on very sensitive individuals. It was used on the skin of newly born babies without any ill after-effects.

Wounds treated with iodocholeate solutions heal much faster than those treated with Tincture of Iodine. The same is true when iodocholeate is applied on the mucous membrane. When it was given internally to experimental animals, no damage could be found on the mucosa of the stomach.

On account of the low volatility the iodocholeate has a much more prolonged action than the tincture. The technique as described by Etchells and Fabian (3) was used to demonstrate the absence of tissue damage on guinea pigs. A 2.3% Tincture of Iodine was compared with an iodocholeate solution of same iodine content. Strong necrosis appeared on the surface exposed to the tincture, but no visible effect could be noticed on the iodocholeate-exposed area.

Experiments were made on human arms, comparing Tincture of Iodine with an iodocholeate solution of same strength. In both cases a square pad of gauze was soaked with the same amount of the solutions, applied to the arm, and kept under bandages for ten hours. A picture was taken 36 hours after treatment and shows the effect of both solutions: a strong necrosis from the tincture, and practically no effect from the iodocholeate.

The effect of Tincture of Iodine and of an iodocholeate solution, when given internally by means of a stomach tube, to rabbits was demonstrated. There is practically no visible difference between the untreated stomach and the iodocholeate-treated one, but the tincture-treated stomach shows heavy injuries to the stomach linings and the stomach wall.

The comparison in the effect of a diluted Tincture of Iodine and an iodocholeate solution of the same strength was shown on rabbits' eyes. The iodocholeate-treated eye showed very little difference compared with the other eye not treated, whereas the tincture-treated eye showed heavy damage and was definitely lost.

As the iodocholeates differ in so many ways with a tincture of iodine, they offer many new opportunities for their use in pharmacy. On account of their low volatility the iodocholeates can be used for impregnation of surgical gauze, pads and tampons.

Dry powder containing iodocholeate has been prepared. The powder is odorless, of amber color, and its content of active iodine remains stable for years and is always demonstrable by starch solution. Comparative test with iodoform and thymol iodide show a very much higher germicidal effect on the iodocholeate powder. Also ointments and dental cream have been prepared.

At the present time iodine does not have the place in Surgery, Dermatology and Obstetrics, which it should have according to its merits; other very much less valuable germicides occupy its place. The drawbacks to a wider use of iodine of the type of the Tincture are their destructive action on the skin, the high volatility, its affinity for organic matter, resulting in reduction or sometimes complete destruction of the germicidal power, its painfulness in wounds and retardation of the healing process. With these factors eliminated, the possibility for the use of iodine widens considerably.

More could be said about the chemistry, pharmacology, etc., of this compound, but this will be left to another report.

The author expresses the hope that the iodocholeate will find a place where the tincture fails, and that it may become a useful contribution to the present means of fighting infection.

REFERENCES.

(1) *Ber.*, 20, 688 (1877) and *Z. physik. Chem.*, 16, 156 (1895).

(2) U. S. Food and Drug Administration Methods for Testing Antiseptics and Disinfectants, *Circular* 198, pages 13 and 15.

(3) Etchells and Fabian, *J. Ind. Hyg.*, 17, 298–300 (Nov. 1935).

Contributors should get in touch with the officers of the Sections promptly—see page IX, Advertising Section for list of officers.

A COMPARISON OF SPECTROPHOTOMETRIC AND BIOLOGICAL ASSAYS FOR VITAMIN A.*

BY CHARLES L. BARTHEN AND CLIFFORD S. LEONARD.[1]

A great many articles have appeared in the literature concerning the various advantages and comparative accuracy of the colorimetric, spectrographic and biological methods of assays for Vitamin A. However, attempts to confirm some of the published data by collaborated studies have met with only partial success.

As Vitamin A is a nutritional factor, it is the general opinion, that the logical measure of Vitamin potency is the biological response as determined by biological assay. The present U. S. P. Method of Assay for Vitamin A is a decided improvement over previous biological methods. Nevertheless, the inaccuracy due to variance in biological response, and other difficulties encountered in conducting a biological assay, as well as the time required and the expense involved, are sufficient reasons for the development and adoption of a satisfactory alternate for the biological assay.

Having available extensive facilities for conducting biological assays and a considerable experience in their interpretation, together with a large variety of Vitamin A bearing substances, physical equipment was installed so that this laboratory would be in a position to make the necessary correlations of biological assays with the physical estimations.

British and other workers claim that the Vitamin A content of Cod Liver Oil and other Fish Liver Oils can be determined by means of the absorption at 3280 Angstrom units. In view of these claims, we have conducted a comprehensive series of examinations of Cod Liver Oil, Fish Liver Oils and their Concentrates.

SPECTROMETRIC STUDIES.

Methods and Apparatus.—The results obtained in British Laboratories with the Hilger Vitameter were so promising and aroused so much interest that several laboratories in the United States purchased and studied this instrument. The Vitameter is supposed to be a simplified optical absorption meter for measuring the absorption at 328 millimicrons or 3280 Angstrom units. However, it was difficult to establish conditions which would insure any degree of accuracy in the readings obtained with this instrument. Certain inherent faults of the Vitameter caused it to give E values which could not be checked satisfactorily with results obtained in other places, or in repeated analyses of the same specimen. Therefore, it was decided to obtain a quartz spectrograph and place it in comparison with the Vitameter.

The Hilger small quartz spectrograph with "Spekker" photometer was chosen because of its quality of optical and mechanical design, its comparatively low cost and the facilities it offered in regard to convenience in operation and conservation of time in obtaining results. A quartz Direct Current mercury vapor arc was used to

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[1] White Laboratories, Inc., Newark, N. J.

test from time to time the accuracy of the wave-length scale of the Spectrophotometer. A Bausch and Lomb photoelectric densitometer was installed to correct visual dotting of absorption curves and thus to make more accurate readings of the entire ultraviolet absorption curve of the plates. The densitometer was supplied with a Julius suspension for the Leeds and Northrop galvanometer, to minimize effects of vibration.

The work was housed in a building separated from factory operations, for it was felt that there was too much vibration in the main laboratory building for proper maintenance of adjustment of the delicate physical instruments. As it was found that large fluctuations of temperature, such as the diurnal changes of summer temperatures, caused serious aberrations of results, an air conditioning system was installed to insure a constant temperature of 20° C. (68° F.), the point for which all volume apparatus is calibrated.

Photographic Methods.—The plates used were Eastman 33 (Process) Plates. The developer was an Elon-Hydroquinone formula recommended by the Eastman Kodak Laboratory. Simple tray development was standardized as to time and temperature (4 minutes at 20° C.). The fixing bath was the chrome alum bath described in Eastman Kodak Company literature. Two plates were usually taken for each specimen. A first plate covered density settings of the photometer from 0.0 to 1.5 by steps of 0.1. This gave a plate from which the absorption curve of the material in the ultraviolet could later be read if desired. Finding on this plate (wet) the nearest to a matching strip, a second plate was taken covering densities 0.1 above and below this strip, with photometer settings 0.02 or 0.03 apart. From this 2nd plate the matching density at 3280 Angstrom units was determined.

Calibration of the Instrument.—The Spekker photometer was standardized by comparing the value obtained at 3130 Angstrom units for standard potassium chromate solution (read against distilled water in the standard cell) with the molar extinction at 3130 recorded in the literature (1).

Choice of Solvent.—The use of either ethyl alcohol or cyclohexane has been recommended for making dilutions in this type of work. Experiments were conducted to compare these solvents with isopropanol. Unsaponifiable fractions obtained by the A. O. A. C. method from U. S. P. Reference Oil were diluted with the three different solvents. Readings obtained immediately after dilution were compared with results obtained after allowing the solutions to stand at 20° C. for 24 hours or longer. Initially, all the solvents gave approximately the same results on any one instrument (Vitameter or Spectrophotometer). On standing, there is a definite decrease in the E value in cyclohexane and ethyl alcohol solutions. However, in isopropanol solutions, there is no diminution in the E value during one week's time. Dilute solutions of cod liver oil concentrates have been kept in this solvent for over a month without loss of E value. Isopropanol transmits a satisfactory band of light to 2300 Angstrom units.

It was found necessary to use 99% isopropanol since more dilute grades would not dissolve some of the samples tested. In view of the above-mentioned advantages and the low cost, this solvent was adopted as a diluent in all determinations.

Preparation of the Specimens.—It was the consensus of opinion that, in cases of oils which contain less than 10,000 Vitamin A units per Gm., the E value of the oil

should be determined on the unsaponifiable fraction. However, in cases where the determinations are made on the whole oil, approximately one Gm. of the oil is weighed directly into a 100-cc. volumetric flask and diluted to volume with 99% isopropanol. The E value is then determined on the proper aliquot dilution.

The method of saponification adopted was a slight modification of the procedure recommended by F. W. Irish (Associate Referee of the A. O. A. C.) which is as follows: Two grams of oil are saponified with 20 cc. of $N/2$ freshly prepared alcoholic KOH, by boiling until clear on a water-bath (time 7–10 minutes); forty cc. of distilled water are added, part being poured down the reflux condenser, the solution cooled, transferred to a Squibb type separatory funnel and extracted with two 50-cc. quantities of peroxide-free ether. The ethereal extracts are washed first with two 20-cc. portions of distilled water, then with two 20-cc. portions of $N/2$ KOH and again with two 20-cc. portions of water while rotating gently without shaking. Patience must be exercised to wait for breaking of any emulsion at the interface. The ethereal solution is then shaken thoroughly with two 20-cc. portions of distilled water, after which it is filtered through a dry paper into a flask, transferred with rinsings with ether into a distilling bulb in a bath not over 54° C. (130° F.) and the ether evaporated nearly to dryness. The residue is immediately dissolved in 99% isopropanol,[1] transferred with rinsing to a 100-cc. volumetric flask and made to volume. From this dilution representing two Gm. of the initial specimen as weighed out, aliquots are taken with accurately calibrated pipettes, to make the proper dilutions for satisfactory reading on the particular instrument in use.

The Vitameter reading was always taken first, ten observations being averaged, the eye error of the operator added and the $E^{1\%}_{1\ cm.}$ calculated from the optical density and the percentage strength of the dilution. The Vitameter read visually was found to give reasonable results only within the range 0.60 to 0.80 of density (without eye error). From the results obtained with the Vitameter, an estimate can be made as to the proper dilution to employ for the Spectrophotometer. The latter instrument gives most accurate readings at a density of 1.0 to 1.2. The calculations of the $E^{1\%}_{1\ cm.}$ are made in the same manner as for the Vitameter. For the above-mentioned reasons, it is our regular procedure to obtain a Vitameter E value and a Spectrophotometer E value for each specimen examined. The equivalent in biological U. S. P. units is calculated by multiplying the E values by the proper conversion factor for each instrument.

Determination of the U. S. P. Reference Oil Conversion Factors.—Ten different samples of the U. S. P. Reference Oil were saponified and the E values determined on the unsaponifiable fraction according to the method given above. The ten spectrophotometer and ten vitameter results were averaged as shown in Table I. The quotients obtained by dividing 3000 (the official number of units present in U. S. P. Reference Oil) by the E values obtained on each instrument are the conversion factors employed, namely, 1948 for the Vitameter and 2222 for the Spectrophotometer. As may be noted in the table, the two instruments do not give the same result.

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[1] The high coefficient of expansion of isopropanol makes temperature control an important factor.

TABLE I.—U. S. P. REFERENCE OIL FOR VITAMIN A, $E^{1\%}_{1\ cm.}$ AND FACTORS.

Vitameter.	Spectrophotometer.
1.51	1.34
1.54	1.35
1.50	1.39
1.52	1.35
1.52	1.32
1.54	1.33
1.57	1.32
1.54	1.32
1.56	1.37
1.59	1.37
1.54 = Average	1.35 = Average
3000/1.54 = 1948 = Vitameter factor.	3000/1.35 = 2222 = Spectrophotometer factor.

Difficulties Encountered with the Vitameter.—The chief difficulty with this instrument is that the filter is not truly a monochromator. It transmits a band of light ranging from about 2900 to 3900 Angstrom units. This is true in spite of the fact that its own Copper arc light source contributes strongest intensity at 3247 and 3274 Angstrom units.

The readings are markedly affected by the changing intensity of light due to the flickering of the arc. This flickering was reduced somewhat by installing a voltmeter in the circuit, maintaining constant voltage and setting the arc gap to the proper distance. The Vitameter is also affected by the aging of the filter, the uviol glass filter cover, the uviol glass cell walls, and the compensating glass. This condition may account for the variation in results obtained in different laboratories. In view of the above, it is obvious that the Vitameter cannot record the same absorption as does the Spectrophotometer at 3280 Angstrom units, as shown in Table I. This same deviation is shown when the Vitameter Standard Glass is measured in the Spectrophotometer. After observing the frequency of false results with the Vitameter, we decided to employ it only as an instrument for first approximation, for determining the correct dilution which will be in the readable range of the spectrophotometer, and thus save spectrum plates and time.

Advantages of the Spectrophotometer.—The Spectrophotometer gives results which can be confirmed in other laboratories. The Spectrophotometer plates afford a permanent record of the determination. Limits of error for determinations by this method at various levels of E values are cited in the 1936 Addendum to the British Pharmacopœia of 1932 (page 91). In repeated determinations of the same specimens, this laboratory has obtained results, which check with a maximum deviation of $\pm 4\%$.

Ultraviolet Absorption Curves of Various Fish Oils and Concentrates.—From the plates, we have read the absorption curves in the ultraviolet for various fish oils and concentrates. There was observed in the curves of Concentrates, or unsaponifiable fractions, a low point, or minimum of absorption around 3750 Angstrom units. Some fish oils read as whole oils show a plateau around the region of 3750 Angstrom units, while others, supposed to be from the same species, show a minimum. Occasionally, the curve of a whole oil will rise toward the far ultraviolet with no depression in the curve but only a slight inflection.

In many instances, the peak is not at 3280 Angstrom units, but may shift as far in the ultraviolet, as 3180 Angstrom units.

The maximum of absorption at the peak may be as much as 10% higher than the reading at 3280 Angstrom units. In view of the specific instructions given in the official methods of the League of Nations Vitamin Conference Committee and the British Pharmacopœia Addendum, that the absorption should be measured at the wave-length of 3280 Angstrom units, all our determinations were made at this specified wave-length.

The Vitameter E values and the Spectrophotometer E values of approximately 1000 specimens (representing a large variety of Vitamin A bearing substances) have been determined in this laboratory. However, in this particular study, we have only considered the results obtained with the specimens, the Vitamin A potencies of which were determined by means of both the Spectrophotometer and Biological assays. Furthermore, the only Spectrophotometric determinations considered were those conducted subsequent to the period of experimentation and after all the adverse conditions (such as electric current, light and temperature) in the Physics Laboratory had been corrected.

COMMENT ON BIOLOGICAL ASSAYS.

Under the most favorable conditions, biological assays of Vitamin A potency cannot be accurate, because of the many variable factors which may cause a deviation in the results. From the many opinions expressed in the literature, a conservative estimate of the error in biological assays is approximately ± 20%; although some laboratories claim they can check their own biological assays within a deviation of ± 10%.

There are many difficulties encountered by biological laboratories in conducting Vitamin A assays according to the method outlined in the U. S. P. XI. In discussions with bio-chemists representing a number of different laboratories, one question that invariably arises is: "When is a rat really suitable for the assay period?" The U. S. P. states that "a rat shall manifest evidence of Vitamin A deficiency characterized by declining weight and/or ophthalmia." In the event *Declining Weight* is the criterion employed, and the prescribed seven-day period, as outlined in the definition for *Declining Weight*, is strictly adhered to, disastrous conditions are likely to occur in that a great number of animals will not survive the assay period. Therefore, the opinion has been expressed, that the period should be shortened or the definition of *Declining Weight* modified.

Furthermore, the varying degrees in the pathological condition of the rats at the beginning of the assay period, affect the food consumption and the consequent weight response. For this reason there seems to be no definite agreement as to whether the gain in weight shall be measured according to the present U. S. P. specifications or from the point of resumption of growth.

It is also the opinion of those interviewed that the U. S. P., in specifying that the average weight gain of the assay group shall be equal to or greater than the average weight gain of the Reference group, does not permit or allow a sufficient tolerance for the variation in biological response.

In view of the foregoing, the results of biological assays employed in this study are based on our interpretation of the present U. S. P. method of assay for Vitamin

TABLE II.—COD LIVER OILS.

No.	Description.	Spectrophotometer. E Value.	Factor.	Equivalent in U. S. P. Units.	Units Determined by Biol. Assay.	% Difference.*
	Non-destearinated					
1	Whole oil	0.370	2222	822	800	+2.75
	Unsapon. fraction	0.351	2222	780		−2.50
2	Destearinated					
	Whole oil	0.460	2222	1,022	1,000	+2.20
	Unsapon. fraction	0.425	2222	944		−5.60
3	Non-destearinated					
	Whole oil	0.698	2222	1,551	1,500	+3.40
	Unsapon. fraction	0.660	2222	1,467		−2.20
4	Non-destearinated					
	Whole oil	0.797	2222	1,771	1,600	+10.69
	Unsapon. fraction	0.723	2222	1,607		+0.44
5	Non-destearinated					
	Whole oil	0.671	2222	1,491	1,600	−6.81
	Unsapon. fraction	0.703	2222	1,562		−2.38
6	Non-destearinated					
	Whole oil	0.674	2222	1,498	1,600	−6.38
	Unsapon. fraction	0.746	2222	1,658		+3.62
7	Non-destearinated					
	Whole oil	0.777	2222	1,726	1,700	+1.53
	Unsapon. fraction	0.798	2222	1,773		+4.29
8	Non-destearinated					
	Whole oil	0.764	2222	1,698	1,700	−0.12
	Unsapon. fraction	0.774	2222	1,720		+1.18

TABLE II.—*Continued.*

No.	Description.	Spectrophotometer. E Value.	Factor.	Equivalent in U. S. P. Units.	Units Determined by Biol. Assay.	% Difference.*
9	Non-destearinated					
	Whole oil	0.672	2222	1,493	1,700	−12.18
	Unsapon. fraction	0.759	2222	1,686		−0.82
10	Non-destearinated					
	Whole oil	0.764	2222	1,698	1,700	−0.12
	Unsapon. fraction	0.800	2222	1,778		+4.59
11	Destearinated					
	Whole oil	0.845	2222	1,878	1,750	+7.31
	Unsapon. fraction	0.765	2222	1,700		−2.86
12	Non-destearinated					
	Whole oil	0.790	2222	1,755	1,900	−7.63
	Unsapon. fraction	0.818	2222	1,818		−4.32
13	Non-destearinated					
	Whole oil	0.878	2222	1,951	2,000	−2.45
	Unsapon. fraction	0.798	2222	1,773		−11.35
14	Non-destearinated					
	Whole oil	0.824	2222	1,831	2,200	−16.77
	Unsapon. fraction	0.984	2222	2,186		−0.64
15	Non-destearinated					
	Whole oil	1.64	2222	3,644	4,000	−8.90
	Unsapon. fraction	1.63	2222	3,621		−9.45
16	Non-destearinated					
	Whole oil	4.53	2222	10,066	10,000	+0.66
	Unsapon. fraction	4.42	2222	9,821		−1.79
17	Reference oil					
	Whole oil	1.43	2222	3,177	3,000	+5.90
	Unsapon. fraction	1.30	2222	2,889		−3.70
	Average per cent difference of the whole oils				=	−1.58
	Average per cent difference of the unsaponifiable fractions				=	−1.97

* The figures in this column represent the per cent that the units, calculated from the Spectrophotometric E values, are more or less than the units determined by biological assay.

A. In instances where other laboratories assayed the same material, their results confirm our results within what may be considered a permissible biological variance.

COMPARATIVE DATA.

In Table II are shown the results of the Spectrophotometric and Biological assays for Vitamin A of 17 samples of Cod Liver Oil, representing shipments received from all parts of the world (England, Iceland, Japan, Newfoundland, Norway and Russia). It will be noted that the Spectrophotometric determinations are of the whole oils as well as of their unsaponifiable fractions, whereas the Bio-assays are of the whole oils only. The number of units as calculated from the Spectrophotometric E values averaged 1.58% less in the case of whole oils and 1.97% less in the case of unsaponifiable fractions, than those determined by Bio-assays.

The differences between the E values obtained with the whole oils and those obtained with the unsaponifiable fractions are not sufficient to warrant the practice of conducting the determinations with the unsaponifiable fractions.

The oils enumerated in Table II conformed with all the requirements of the U. S. P. and contained less than 1.2% Free Fatty Acids (calculated as Oleic Acid). However, with oils that were rancid or contained more than 2% Free Fatty Acids or impurities such as iron oleate, E values have been obtained with the whole oils which were as much as 25% greater than the E values obtained with their unsaponifiable fractions. Therefore, in cases similar to those mentioned, it would be advisable and more accurate to determine the E value of the unsaponifiable fraction.

In Table III are shown the results of the Spectrophotometric and Biological assays for Vitamin A of nine samples of Halibut Liver Oil representing shipments received from various suppliers. The number of units as calculated from the Spectrophotometric E values averaged 2.85% less than those determined by Bio-assays.

TABLE III.—HALIBUT LIVER OILS.

No.	E Value.	Spectrophotometer. Factor.	Equivalent in U. S. P. Units.	Units Determined by Biol. Assay.	% Difference.*
1	26.8	2222	59,550	60,000	− 0.83
2	36.5	2222	81,103	90,000	− 9.89
3	36.1	2222	80,214	90,000	−10.87
4	28.8	2222	63,994	60,000	+ 6.66
5	35.1	2222	77,992	80,000	− 2.51
6	29.5	2222	65,549	60,000	+ 9.25
7	38.2	2222	84,880	84,000	+ 1.05
8	86.0	2222	191,092	216,000	−11.53
9	33.5	2222	74,437	80,000	− 6.95
				Average per cent difference =	− 2.85

* The figures in this column represent the per cent that the units, calculated from the Spectrophotometric E values, are more or less than the units determined by biological assay.

In Table IV are shown the results of the Spectrophotometric and Biological assays for Vitamin A of 16 samples of High Potency Fish Liver Oil Blends representing shipments received from various suppliers. The number of units as calculated from the Spectrophotometric E values averaged 1.68% less than those determined by Bio-assays.

In Table V are shown the results of the Spectrophotometric and Biological assays for Vitamin A of 11 samples of Vitamin A and D Concentrates prepared from Cod Liver Oil and other Fish Liver Oils in this laboratory. The number of units as calculated from the Spectrophotometric E values averaged 4.03% more than those determined by Bio-assays.

TABLE IV.—HIGH POTENCY FISH LIVER OIL BLENDS.

No.	E Value.	Spectrophotometer. Factor.	Equivalent in U. S. P. Units.	Units Determined By Biol. Assay.	% Difference.*
1	17.5	2222	38,885	40,000	− 2.79
2	9.76	2222	21,687	20,000	+ 8.44
3	11.5	2222	25,553	25,000	+ 2.21
4	17.0	2222	37,774	40,000	− 5.57
5	29.3	2222	65,105	75,000	−13.19
6	11.2	2222	24,886	25,000	− 0.46
7	15.5	2222	34,441	32,000	+ 7.63
8	39.1	2222	86,880	80,000	+ 8.60
9	81.0	2222	179,982	175,000	+ 2.85
10	35.8	2222	79,548	90,000	−11.61
11	8.27	2222	18,376	20,000	− 8.12
12	11.9	2222	26,442	28,000	− 5.56
13	59.5	2222	132,209	137,000	− 3.50
14	70.7	2222	157,095	170,000	− 7.59
15	60.1	2222	133,542	136,000	− 0.18
16	89.5	2222	198,869	195,000	+ 1.98
				Average per cent difference =	− 1.68

* The figures in this column represent the per cent that the units, calculated from the Spectrophotometric E values, are more or less than the units determined by biological assay.

TABLE V.—CONCENTRATES.

No.	E Value.	Spectrophotometer. Factor.	Equivalent in U. S. P. Units.	Units Determined by Biol. Assay.	% Difference.*
1	44.3	2222	98,435	100,000	− 1.57
2	79.3	2222	176,205	170,000	+ 3.65
3	69.1	2222	153,540	140,000	+ 9.67
4	30.5	2222	67,771	60,000	+12.95
5	9.42	2222	20,931	20,000	+ 4.66
6	30.6	2222	67,993	60,000	+13.32
7	22.3	2222	49,551	60,000	−17.41
8	28.5	2222	63,327	60,000	+ 5.55
9	75.8	2222	168,428	180,000	− 6.43
10	29.4	2222	65,327	60,000	+ 8.79
11	18.0	2222	39,996	36,000	+11.10
				Average per cent difference =	+ 4.03

* The figures in this column represent the per cent that the units, calculated from the Spectrophotometric E values, are more or less than the units determined by biological assay.

The difference (as shown in Tables II, III, IV and V) between the number of units calculated from the Spectrophotometric E values and those determined by Bio-assays is not significant when compared with the variation in biological response.

In calculating the equivalent in International units from the Spectrophotometric E values, the Addendum 1936 to the British Pharmacopœia 1932 has accepted provisionally 1600 as the conversion factor. Some laboratories in the United States employ 1600 as a conversion factor in calculating the equivalent in U. S. P. units from the E value. Whether 1600 is the correct figure to employ as a conversion factor is a controversial subject in England and United States. In this connection, it is apropos to quote Pritchard, *et al.* (2):

> "The value of 1600 recommended by the International Conference of 1934 represents a useful compromise, but careful estimates of the conversion factor on different preparations and in different laboratories may vary over the range 700–2500 and it remains uncertain how far the discrepancies are due to inaccuracy in the

biological assays and how far to other contributory causes of a more fundamental nature. The discrepancies appear, however, to be outside any known experimental error."

CONCLUSIONS.

In view of the data submitted in this paper, the suggested procedure which will yield more significant figures and tend to obviate the variances in the results obtained in different laboratories, is:

Each laboratory should determine the E value of the U. S. P. Reference Oil. The quotient obtained by dividing 3000 (the official number of units in one Gm. of Reference Oil) by the E value of the Reference Oil, would be the correct conversion factor for the particular instrument employed. The product obtained by multiplying the E value by the proper conversion factor is the equivalent in biological U. S. P. units in one Gm. of the material examined.

Sufficient data are presented to warrant the adoption (by the U. S. P.) of a Spectrophotometric method for the determination of the Vitamin A content of Cod Liver Oil and other Fish Liver Oils, as an alternate for the Biological assay. The obvious advantages of the Spectrophotometric determinations over Biological assay are:

Greater degree of accuracy with consequent closer agreement in the results obtained in different laboratories
Greater convenience
Conservation of time and expense.

REFERENCES.

(1) Weigert, "Die Optische Methoden der Chemie," Leipsig, page 234 (1927).

(2) Pritchard, Harry, and Wilkinson, Harry, "A Discrepancy between Biological Assays and Other Methods of Determining Vitamin A," *Biochem. J.*, Vol. 31, No. 2, 259 (February 1937).

AMERICAN INSTITUTE OF CHEMISTS.

The American Institute of Chemists held its annual meeting May 15th, in the Chemists Club, New York, followed by a dinner at which the medal of the American Institute of Chemists, awarded annually for outstanding service to the science of chemistry, was presented to Dr. James F. Norris, director of the research laboratory in organic chemistry at the Massachusetts Institute of Technology.

The Willard Gibbs Gold Medal of the Chicago section of the American Chemical Society, one of the highest distinctions in chemical science, was conferred on Dr. Herbert Newby McCoy, internationally known for his achievements in radioactivity. Dr. Paul Van Cleef, chairman of the section, presided and delivered an address on "The Inspiration of Willard Gibbs." The presentation speech was by Dr. Edward R. Weidlein, director of the Mellon Institute of Industrial Research, and president of the American Chemical Society.

The American Chemical Society sponsored the Colloid Symposium which was held June 10th to 12th at the University of Minnesota and Mayo Clinic. The committee on colloid science of the National Research Council participated.

HOSPITAL PROGRESS.

The special directory number of *Hospital Progress*, which is the official organ of the Catholic Hospital Association of the United States and Canada, has issued a very valuable special directory number. The foreword is "The Catholic Hospital and School of Nursing at the End of 1936." The tables and directories take up 89 pages of the special number.

"The Story of an Old Book Cover," by Sister Mary E. Xavier, of Mount Mary College, Milwaukee, is a leading article of *The Science Counselor* of the June number; the *Foreword* is by **Dr. Edward Kremers.** The old volume was printed in 1573, and is an interesting translation of the parchment.

REPORT OF THE VITAMIN ASSAY COMMITTEE OF THE AMERICAN DRUG MANUFACTURERS' ASSOCIATION—TWENTY-SIXTH ANNUAL MEETING—MAY 1937.

I—THE PRACTICAL APPLICATION OF THE SPECTROPHOTOMETRIC METHOD FOR ASSAY OF VITAMIN A.*

BY A. D. HOLMES, A. BLACK, C. R. ECKLER, A. D. EMMETT, F. W. HEYL, C. NEILSEN AND E. J. QUINN.[1]

The biological method (specified by U. S. P. XI) for the assay of the Vitamin A content of cod liver oil and related products is laborious, time consuming and very expensive. As a consequence, for a number of years investigators and analysts have been seeking for a more rapid, convenient and less expensive method for Vitamin A assays. This search resulted in the development of the so-called Carr-Price (1) antimony trichloride method. This method consists of a comparison of a blue color developed by the reaction of Vitamin A and antimony trichloride in a chloroform solution with standard blue color glasses. The antimony trichloride method for Vitamin A assay has many desirable features and it has been very useful for estimating Vitamin A potency but since other factors may give a blue color it has not been generally accepted as a reliable quantitative method for Vitamin A assay.

A number of investigators found in their studies of absorption spectra that Vitamin A gives a characteristic curve in the ultraviolet region with the peak at 3200 Angstrom units. Accordingly by measuring the absorption of ultraviolet light at 3280 Angstrom units an estimate could be made of the Vitamin A.

Unfortunately the usual spectrograph instruments on which these investigations were conducted are far too expensive, and besides their use necessitated highly experienced and capable operators. Consequently this type of determination of Vitamin A seemed unsuitable for general practical Vitamin A assay. However, in 1933 a specially devised and relatively inexpensive instrument, "Vitameter A," was manufactured by the Adam Hilger, Ltd., of London.

Since this instrument seemed to offer considerable promise for the rapid assay the Vitamin Committee of the American Drug Manufacturers' Association made a preliminary investigation of its value during 1935 particularly for the assay of cod liver oils. Three of the laboratories of the A. D. M. A. Vitamin Committee who made purchases of the instrument and two associate non-member laboratories participated in the study. The results of these 5 workers (2) made on 13 fish liver oils showed that assays could be made with a fair degree of accuracy within an hour or so. Compared with a month or more by the biological test the practical significance of the use of the Vitameter is self-evident—even if the test could be used only as a tentative or suggested index.

About the same time the Association of Official Agricultural Chemists also conducted a study of the value of the Vitameter for assaying cod liver oil. Five samples of cod liver oils previously bio-assayed for their Vitamin A potency were sent to eleven vitamin testing laboratories. The chairman, Dr. Irish (3), reported

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* Presented before the Scientific Section of the American Drug Manufacturers' Association, 26th Annual Meeting, May 1937.

[1] The Vitamin Committee of the American Drug Manufacturers' Association.

that the results obtained by the different laboratories varied from 18% to 32% depending upon which one of the three procedures he outlined was followed.

Therefore, in view of the somewhat promising results obtained in this preliminary investigation with the Vitameter, the A. D. M. A. Vitamin Committee undertook at your recommendation a more extensive study during 1936. This year's program included the assay of thiry-four samples consisting of: 11 cod liver oils, 11 cod liver oil concentrates, 9 halibut liver oils, and 6 so-called "other fish liver oils," 2 halibut liver oil concentrates and 1 sardine body oil. These samples were supplied by different members of the committee and in nearly all instances they represented market products. Of particular interest throughout this report is the fact that Sample 11 is the U. S. P. Reference Cod Liver Oil which has an assigned biologic value of 3000 U. S. P. or International units per Gm.

Two factors, with regard to the equipment and experience of the laboratories, have entered into the problem and should be borne in mind. *First*, the manufacturers have been gradually improving the instruments throughout the past 2 to 3 years. Since the participants in this study have purchased their instruments at various times during this interval it is obvious that there are uncontrolled variations in the equipment. *Secondly*, the finesse in the technique of operating the instrument doubtless varies to a considerable extent with the amount of experience the operator acquires. That is to say no two laboratories have used exactly the same model of Vitameter or have they worked with it for exactly the same length of time. Furthermore, in order to amplify the project, it was decided to accept the coöperation of a few laboratories outside those represented on the committee. In so doing, it has been found that the data thereby contributed introduced in some instances values which were difficult to average into the groupings and therefore these had to be set out, as it were, for individual consideration. In order that these laboratories should be representative they were selected to include academic, federal government and industrial laboratories. The Vitamin Committee is deeply grateful for the generous coöperation extended to it by the Atlantic Coast Fisheries Corporation, Gorton-Pew Fisheries Company Ltd., Health Products Corporation, The Crookes Laboratories, The Norwich Pharmacal Company, The Ohio State University—Department of Chemistry, and the United States Department of Agriculture—Food and Drug Administration. Some of the laboratories were provided with both a Vitameter and a Spectrophotometer. Such laboratories assayed the samples with both instruments.

It is generally believed that the Vitameter gives more reliable results in the assay of oils of high Vitamin A potency than for oils of low potency. Accordingly the eleven cod liver oils were assayed by testing the fluid oil for its Vitamin content and by testing the Vitamin A content of the unsaponifiable portion of the oil.

It was originally intended that the laboratory procedure for conducting the Vitameter assays should be uniform for all the coöperating laboratories. Accordingly each laboratory was asked to conduct the assays as follows:

> "It is hoped that, in each laboratory, two or more persons will make assays of all samples and report their results separately. Preferably use cyclohexane as the solvent but in any case report the solvent used. In preparing solutions add a weighed amount of the product under test to a measured volume of solvent."
>
> "Preferably make Vitameter readings one hour after the solution has been prepared but

in any case report the time interval between preparation of solution and making Vitameter reading. The final 'reading' is to be the average of ten readings, except when the photographic method is used. In making dilutions of the dissolved sample adjust the strength of the solution so that the readings will be between 0.6 and 0.8 on the Vitameter scale. Make two separate assays of the cod liver oils (A) the cod liver oil as such and (B) the unsaponifiable portion of the cod liver oil. Follow Irish (3) method of saponification: 'One gram of oil is saponified with 10 cc. $N/2$ freshly prepared alcoholic KOH, by boiling until clear (time needed 5 minutes). Twenty cubic centimeters of water are added, the whole transferred to a small separator and extracted with two quantities of 25 cc. ether (peroxide free). The ethereal extracts are washed first with water (10–20 cc.) then with 10–20 cc. $N/2$ KOH and again with water, while rotating gently without shaking. The ethereal solution is then shaken thoroughly with two quantities of 10 cc. water, after which it is filtered into a flask, the ether evaporated almost to dryness and the residue dissolved in ethyl alcohol or cyclohexane and made up to the concentration required for the particular instrument in use. A preliminary test on the original oil will indicate the amount both of oil and of solvent which will be necessary.' "

Due to various unforeseen conditions it was necessary for some of the laboratories to modify this procedure somewhat. Laboratory No. 12, which was not provided with suitable electric current, modified their Vitameter by substituting for the copper arc a General Electric S-1 Therapeutic Lamp. It was very fortunate that this modification was attempted since a number of other laboratories have found it inconvenient to provide the proper current for the Vitameter.

Again Laboratory No. 2 found that the continuous use of the Vitameter caused considerable undesirable eyestrain to the operators. This tended to produce variable results. In order to eliminate this factor the instrument was equipped for making photographs of the spectrographic determinations. The procedure was a modification of the method recommended by Notevarp (4). This provides a permanent record of the results of the assays.

Further, the manufacturer of the Vitameter originally recommended chloroform as the solvent for preparing cod liver oils for Vitameter assay. Subsequently cyclohexane was recommended. During this study, tests were made with chloroform, cyclohexane, alcohol, absolute alcohol, isopropyl alcohol, a mixture of 80% alcohol and 20% cyclohexane, and a mixture of 90% alcohol and 10% cyclohexane as solvents. Satisfactory results were obtained with cyclohexane, isopropyl alcohol, alcohol and absolute alcohol but solutions prepared with chloroform tended to lose their Vitamin A potency on standing.

The results obtained from the spectrophotometric assay of the vitamin A content of over fifteen thousand solutions prepared from the samples under consideration are presented in the following six tables:

Table I: Results of Vitameter Assays—"E Values"—A. D. M. A. Laboratories.

Table II: Results of Vitameter Assays—"E Values"—Coöperating Laboratories.

Table III: Results of Spectrophotometric Assays—"E Values"—A. D. M. A. and Cooperating Laboratories.

Table IV: Comparison of Vitameter and Spectrophotometer Values from Same Laboratories—"E Values."

Table V: Deviation of the Respective Vitameter Values from the Average—A. D. M. A. Laboratories.

Table VI: Vitameter Data—Applying the Correction Factor for Each Laboratory.

TABLE I.—RESULTS OF VITAMETER ASSAYS—"E VALUES," A. D. M. A. LABORATORIES.

Sample.	Lab. No. 1.	Lab. No. 2.	Lab. No. 3.	Lab. No. 4.	Lab. No. 5.	Lab. No. 6.	Lab. No. 7.	Max.	Min.	Av.
					Cod Liver Oils.					
1	1.37	1.36	1.71	1.73	1.64	1.61	1.70	1.73	1.36	1.59
2	0.76	0.79	1.15	0.93	1.05	0.87	1.31	1.31	0.76	0.98
3	0.93	0.99	1.20	0.95	1.12	1.12	1.41	1.41	0.93	1.10
4	1.45	1.43	1.61	1.74	1.85	1.76	1.69	1.85	1.43	1.65
5	1.10	1.12	1.35	1.35	1.39	1.38	1.58	1.58	1.10	1.32
6	1.33	1.45	1.48	1.57	1.64	1.60	1.69	1.69	1.33	1.54
7	1.48	1.65	1.72	1.86	1.71	1.84	1.70	1.86	1.48	1.71
8	1.61	1.69	1.69	1.98	1.92	1.91	2.07	2.07	1.61	1.84
9	0.83	0.83	1.14	1.05	1.04	0.97	1.22	1.22	0.83	1.01
10	1.09	1.07	1.34	1.36	1.41	1.36	1.54	1.54	1.07	1.31
11	1.44	1.54	1.65	1.60	1.56	1.79	1.66	1.79	1.44	1.61
					Cod Liver Oil (Unsaponifiable Portion).					
1	1.16	1.06	1.44	1.34	1.54	1.46	1.68	1.68	1.06	1.38
2	0.74	0.69	0.91	0.79	0.94	0.76	1.30	1.30	0.69	0.88
3	0.88	0.84	0.93	0.93	1.09	1.02	1.48	1.48	0.84	1.02
4	1.34	1.22	1.31	1.38	1.59	1.69	1.64	1.69	1.22	1.45
5	0.98	0.75	1.24	1.06	1.24	1.20	1.52	1.52	0.75	1.14
6	1.24	1.32	1.25	1.37	1.51	1.51	1.68	1.68	1.24	1.41
7	1.24	1.38	1.27	1.40	1.51	1.59	1.70	1.70	1.24	1.44
8	1.43	1.38	1.55	1.65	1.67	1.73	2.08	2.08	1.38	1.64
9	0.74	0.77	0.85	0.92	1.04	0.85	1.22	1.22	0.74	0.91
10	0.98	0.91	0.89	1.06	1.34	1.16	1.52	1.52	0.89	1.12
11	1.37	1.38	1.40	1.21	1.54	1.60	1.68	1.68	1.21	1.45
					Cod Liver Oil Concentrates.					
12	23.99	22.22	21.4	28.18	26.30	32.20	40.00	40.00	21.40	27.75
13	18.56	18.48	16.9	25.78	22.80	25.94	30.00	30.00	16.90	22.64
14	18.32	20.27	19.1	23.98	24.00	26.19	30.50	30.50	18.32	23.19
15	64.46	63.52	62.7	81.69	73.40	102.65	82.00	102.65	62.70	75.77
16	16.25	28.50	16.5	19.50	18.10	23.76	23.00	23.76	16.25	20.80
					Halibut Liver Oils.					
17	37.56	34.90	34.0	43.40	37.60	46.46	44.70	46.46	34.00	39.80
18	32.13	30.38	28.6	35.08	34.10	38.25	42.50	42.50	28.60	34.43
19	17.68	16.50	15.5	19.10	18.27	22.67	20.25	22.67	15.50	18.57
20	49.56	51.60	50.1	59.56	57.55	60.29	75.00	75.00	49.36	57.67
21	66.25	59.76	70.5	87.30	73.30	85.55	100.00	100.00	59.76	77.52
22	15.65	16.59	14.6	21.79	17.10	22.80	21.50	22.80	14.60	18.57
23	24.03	28.03	28.4	41.50	31.02	34.70	37.00	41.50	24.03	32.10
24	43.87	41.66	45.1	55.12	45.87	53.66	67.50	67.50	41.66	50.39
25	53.68	52.63	58.1	70.90	59.72	78.00	80.00	80.00	52.63	64.72
					Other Fish Liver Oils.					
26	87.25	91.32	88.4	100.73	92.35	109.61	130.0	130.00	87.25	99.95
27	48.51	54.01	51.0	66.75	56.65	59.90	76.0	76.00	48.51	58.97
28	76.88	74.74	72.8	90.31	72.45	114.16	103.3	114.16	72.45	86.38
29	32.54	37.97	36.9	46.77	37.75	48.79	57.5	57.50	32.54	42.60
30	53.68	59.16	54.9	85.19	61.85	77.70	77.5	77.70	53.68	67.14
31	35.26	35.71	39.5	46.80	40.25	56.42	60.0	60.00	35.26	44.85

				Halibut Liver Oil Concentrate.						
32	562.00	724.50	581.3	912.00	742.00	779.00	725.0	912.00	562.00	717.96
				Cod Liver Oil Concentrate and Halibut Liver Oil Mixture.						
33	34.09	36.36	39.3	39.38	33.60	48.40	43.0	48.40	33.60	39.16
				Sardine Body Oil.						
34	0.41	0.48	0.4	0.63	0.58	0.66	1.3	1.30	0.40	0.64

TABLE II.—RESULTS OF VITAMETER ASSAYS—"E VALUES," COÖPERATING LABORATORIES.

Sample.	Lab. No. 8.	Lab. No. 9.	Lab. No. 10.	Lab. No. 11.	Max.	Min.	Av.	Lab. No. 12.
				Cod Liver Oils.				
1	1.07	1.48	1.57	1.33	1.57	1.07	1.36	0.37
2	0.60	0.95	0.85	0.76	0.95	0.60	0.79	0.18
3	0.68	1.18	1.26	0.92	1.26	0.68	1.01	0.24
4	1.08	1.72	1.55	1.55	1.72	1.08	1.48	0.38
5	0.75	1.76	1.18	1.06	1.76	0.75	1.19	0.31
6	1.13	1.52	1.52	1.51	1.52	1.13	1.42	0.41
7	1.27	1.95	1.45	1.84	1.95	1.27	1.63	15.40
8	1.37	2.08	1.64	1.78	2.08	1.37	1.72	0.37
9	0.72	0.97	1.05	0.97	1.05	0.72	0.93	0.18
10	1.00	1.31	1.42	1.19	1.42	1.00	1.23	0.32
11	1.06	1.04	1.46	1.56	1.56	1.04	1.28	0.37
				Cod Liver Oil (Unsaponifiable Portion).				
1			1.56	1.32				0.18
2			1.00	0.75				0.17
3			0.86	0.92				0.15
4			1.10	1.52				0.19
5			0.85	1.05				...
6			1.26	1.49				...
7			1.46	1.72				...
8			1.61	1.70				...
9			0.96	0.94				...
10			1.13	1.15				...
11			1.22	1.49				...
				Cod Liver Oil Concentrates.				
12	16.2	53.2	29.8	26.88	53.2	16.2	31.52	7.80
13	15.4	14.3	21.2	21.88	21.88	14.3	18.20	6.70
14	14.3	7.7	19.1	21.29	21.29	7.7	15.60	6.90
15	63.8	38.5	71.7	73.61	73.61	38.5	61.90	24.00
16	13.5	13.0	19.2	18.20	19.2	13.0	15.98	4.65
				Halibut Liver Oils.				
17	30.1	45.6	38.2	35.6	45.6	30.1	37.4	13.00
18	24.6	31.8	35.6	32.5	35.6	24.6	31.1	10.20
19	13.6	18.8	19.0	16.0	19.0	13.6	16.8	6.80
20	45.0	59.0	56.4	53.4	59.0	45.0	53.5	7.40
21	58.1	75.8	65.7	68.7	75.8	58.1	67.1	10.40
22	12.2	18.1	19.6	15.3	19.6	12.2	16.3	4.75
23	19.3	27.8	34.3	28.3	34.3	19.3	27.4	5.90
24	32.9	42.9	43.3	44.2	44.2	32.9	40.8	8.15
25	46.1	55.6	71.2	58.9	71.2	46.1	58.0	12.60

				Other Fish Liver Oils.				
26	75.1	89.1	90.0	89.1	90.0	75.1	85.8	14.35
27	42.2	49.9	46.8	50.9	50.9	42.2	47.4	13.00
28	61.2	75.9	75.3	80.4	80.4	61.2	73.2	21.00
29	27.2	34.3	44.2	40.3	44.2	27.2	36.5	8.15
30	48.1	65.0	63.4	62.1	65.0	48.1	59.7	21.50
31	28.7	38.8	49.3	40.4	49.3	28.7	39.3	9.80
				Halibut Liver Oil Concentrate.				
32	501.9	1064.0	559.0	748.0	1064.0	501.9	718.23	...
				Cod Liver Oil Concentrate and Halibut Liver Oil Mixture.				
33	28.4	42.0	38.4	44.57	44.57	28.4	38.34	9.10
				Sardine Body Oil.				
34	0.5	0.36	0.73	0.57	0.73	0.36	0.54	0.16

TABLE III.—RESULTS OF SPECTROPHOTOMETER ASSAYS—"E VALUES," A. D. M. A. AND COÖPERATING LABORATORIES.

Sample.	Lab. No. 3.	Lab. No. 9.	Lab. No. 10.	Lab. No. 13.	Lab. No. 14.	Max.	Min.	Av.	Av.*
				Cod Liver Oils.					
1	1.56	1.31	1.37	1.33	1.30	1.56	1.30	1.37	1.59
2	0.96	0.78	0.80	0.81	0.90	0.96	0.78	0.85	0.98
3	1.21	1.18	0.87	0.92	1.00	1.21	0.87	1.04	1.10
4	1.86	1.45	1.14	1.57	2.10	2.10	1.14	1.62	1.65
5	1.31	1.02	0.96	1.08	0.80	1.31	0.80	1.03	1.32
6	1.57	1.28	1.29	1.36	1.00	1.57	1.00	1.30	1.54
7	1.79	1.45	1.21	1.55	1.80	1.80	1.21	1.56	1.71
8	1.83	1.43	1.50	1.40	1.30	1.83	1.30	1.49	1.84
9	1.11	0.78	0.78	0.86	1.10	1.11	0.78	0.92	1.01
10	1.16	1.23	1.16	1.12	1.30	1.30	1.12	1.19	1.31
11	1.71	1.37	1.19	1.58	...	1.71	1.19	1.46	1.61
				Cod Liver Oil (Unsaponifiable Portion.)					
1	1.43	0.72	1.17	1.15		1.43	0.72	1.12	1.38
2	0.92	0.91	0.65	0.67		0.92	0.65	0.79	0.88
3	0.92	0.80	0.75	0.85		0.92	0.75	0.83	1.02
4	1.30	1.29	1.04	1.39		1.39	1.04	1.26	1.45
5	1.17	0.92	0.75	0.98		1.17	0.75	0.96	1.14
6	1.31	0.96	1.09	1.16		1.31	0.96	1.13	1.41
7	1.35	1.31	1.31	1.29		1.35	1.29	1.32	1.44
8	1.54	1.48	1.51	1.28		1.54	1.28	1.45	1.64
9	0.87	0.77	0.83	0.71		0.87	0.71	0.79	0.91
10	0.94	0.79	1.06	0.98		1.06	0.79	0.94	1.12
11	1.42	...	0.99	1.26		1.42	0.99	1.22	1.45
				Cod Liver Oil Concentrates.					
12	20.98	23.30	21.7	24.90		24.90	20.98	22.72	27.75
13	16.13	20.10	18.6	20.00		20.10	16.13	18.71	22.64
14	17.07	18.70	16.5	18.45		18.70	16.50	17.68	23.19
15	67.41	64.30	64.3	62.40		67.41	62.40	64.60	75.77
16	13.49	16.00	15.4	14.45		16.00	13.49	14.84	20.8

Halibut Liver Oils.								
17	30.86	34.70	27.0	33.65	34.70	27.00	31.55	39.80
18	28.09	29.70	26.8	30.75	30.75	26.80	28.84	34.43
19	16.70	16.80	15.5	16.95	16.95	15.50	16.49	18.57
20	46.28	56.20	52.5	57.05	57.05	46.28	53.01	57.67
21	58.38	71.10	56.0	71.05	71.10	56.00	64.13	77.52
22	14.69	16.70	15.7	16.70	16.70	14.69	15.95	18.57
23	25.03	25.30	24.2	26.40	26.40	24.20	25.23	32.10
24	44.60	44.30	35.5	45.75	45.75	35.50	42.54	50.39
25	57.46	58.40	52.9	61.00	61.00	52.90	57.44	64.72
Other Fish Liver Oils.								
26	86.12	87.40	80.9	88.90	88.90	80.90	85.83	99.95
27	49.03	51.20	45.5	52.85	52.85	45.50	49.65	58.99
28	72.72	73.40	76.9	76.25	76.90	72.72	74.82	86.38
29	32.94	33.25	33.3	35.05	35.05	32.94	33.64	42.60
30	50.79	59.30	59.8	57.25	59.80	50.79	56.79	67.14
31	36.51	36.70	31.8	37.00	37.00	31.80	35.50	44.85
Halibut Liver Oil Concentrate.								
32	587.50	620.00	570.0	597.50	620.00	570.00	593.75	717.96
Cod Liver Oil Concentrate and Halibut Liver Oil Mixture.								
33	39.03	37.60	32.7	34.45	39.03	32.70	35.95	39.16
Sardine Body Oil.								
34	0.39	None	0.58	None	0.58	0.39	0.49	0.64

TABLE IV.—VITAMETER AND SPECTROPHOTOMETER BY SAME LABORATORY—"E VALUES," A. D. M. A. AND COÖPERATING LABORATORIES.

Sample.	Lab. No. 3. Vitameter.	Lab. No. 3. Spectrophotometer.	Lab. No. 9. Vitameter.	Lab. No. 9. Spectrophotometer.	Lab. No. 10. Vitameter.	Lab. No. 10. Spectrophotometer.	Av. Vitameter.	Av. Spectrophotometer.
Cod Liver Oils.								
1	1.71	1.56	1.48	1.31	1.57	1.37	1.59	1.41
2	1.15	0.96	0.95	0.78	0.85	0.80	0.98	0.85
3	1.20	1.21	1.18	1.18	1.26	0.87	1.21	1.09
4	1.61	1.86	1.72	1.45	1.55	1.14	1.63	1.48
5	1.35	1.31	1.76	1.02	1.18	0.96	1.43	1.10
6	1.48	1.57	1.52	1.28	1.52	1.29	1.51	1.38
7	1.72	1.79	1.95	1.45	1.45	1.21	1.71	1.48
8	1.69	1.83	2.08	1.43	1.64	1.50	1.80	1.59
9	1.14	1.11	0.97	0.78	1.05	0.78	1.05	0.89
10	1.34	1.16	1.31	1.23	1.42	1.16	1.36	1.18
11	1.65	1.71	1.04	1.37	1.46	1.19	1.38	1.42
Cod Liver Oil (Unsaponifiable Portion).								
1	1.44	1.43			1.56	1.17	1.50	1.30
2	0.91	0.92			1.00	0.65	0.96	0.79
3	0.93	0.92			0.86	0.75	0.90	0.84
4	1.31	1.30			1.10	1.04	1.20	1.17

* Average of Vitameter Assays—See Table I.

5	1.24	1.17			0.85	0.75	1.04	0.96
6	1.25	1.31			1.26	1.09	1.26	1.20
7	1.27	1.35			1.46	1.31	1.36	1.33
8	1.55	1.54			1.61	1.51	1.58	1.53
9	0.85	0.87			0.96	0.83	0.92	0.85
10	0.89	0.94			1.13	1.06	1.01	1.00
11	1.40	1.42			1.22	0.99	1.31	1.21
			Cod Liver Oil Concentrates.					
12	21.4	20.98	53.2	23.30	29.80	21.70	34.80	21.99
13	16.9	16.13	14.3	20.10	21.20	18.60	17.47	18.28
14	19.0	17.07	7.7	18.70	19.10	16.50	15.27	17.42
15	62.7	67.41	38.5	64.30	71.70	64.30	57.63	65.34
16	16.5	13.49	13.0	16.00	19.15	15.40	16.22	14.96
			Halibut Liver Oils.					
17	34.0	30.86	45.6	34.70	38.20	27.0	39.27	30.85
18	28.6	28.09	31.8	29.70	35.60	26.8	32.00	28.20
19	15.5	16.70	18.8	16.80	19.00	15.5	17.77	16.33
20	50.1	46.28	59.0	56.20	56.35	52.5	55.15	51.66
21	70.5	58.38	75.8	71.10	65.70	56.0	70.66	61.83
22	14.6	15.69	18.1	16.70	19.60	15.7	17.43	15.70
23	28.4	25.03	27.8	25.30	34.25	24.2	30.15	24.85
24	45.1	44.60	42.9	44.30	43.30	35.5	43.77	41.47
25	58.1	57.46	55.6	58.40	71.15	52.9	61.62	56.25
			Other Fish Liver Oils.					
26	88.4	86.12	89.1	87.40	89.95	80.9	89.15	84.81
27	51.0	49.03	49.9	51.20	46.80	45.5	49.23	48.58
28	72.8	72.72	75.9	73.40	75.30	76.9	74.67	74.34
29	36.9	32.94	34.3	33.25	44.15	33.3	38.45	33.16
30	54.9	50.79	65.0	59.30	63.40	59.8	61.10	56.63
31	39.5	36.51	38.8	36.70	49.30	31.8	42.53	35.00
			Halibut Liver Oil Concentrate.					
32	581.3	587.50	1064.2	620.00	559.00	570.0	734.80	592.50
			Cod Liver Oil Concentrate and Halibut Liver Oil Mixture.					
33	39.3	39.03	42.0	37.60	38.35	32.70	39.88	36.44
			Sardine Body Oil.					
34	0.4	0.39	0.36	None	0.73	0.58	0.50	0.49

TABLE V.—DEVIATION OF THE RESPECTIVE VITAMETER VALUES FROM THE AVERAGE—PER CENT, A. D. M. A. LABORATORIES.

Sample.	Lab. No. 1.	Lab. No. 2.	Lab. No. 3.	Lab. No. 4.	Lab. No. 5.	Lab. No. 6.	Lab. No. 7.
			Cod Liver Oils.				
1	−13.8	−14.4	+ 7.5	+ 8.8	+ 3.2	+ 1.3	+ 6.9
2	−22.5	−19.4	+17.3	− 5.1	+ 7.2	−11.1	+33.6
3	−15.4	−10.0	+ 5.5	−12.7	+ 1.8	+ 1.8	+27.3
4	−12.1	−13.3	− 2.4	+ 5.5	+12.1	+ 6.7	+ 2.4
5	−16.7	−15.2	+ 2.3	+ 2.3	+ 5.3	+ 4.6	+19.7
6	−13.6	− 5.8	− 3.9	+ 1.9	+ 6.5	+ 3.9	+ 9.9

	7	−13.5	− 3.5	+ 0.6	+ 8.8	0.0	+ 7.6	− 0.6
	8	−12.5	− 8.2	− 8.2	+ 7.6	+ 4.4	+ 3.8	+12.5
	9	−17.8	−17.8	+12.9	+ 3.8	+ 3.0	− 3.8	+10.9
	10	−16.8	−18.3	+ 2.3	+ 3.8	+ 7.7	+ 3.8	+17.6
	11	−10.0	− 3.7	+ 3.1	0.0	− 2.5	+10.6	+ 3.7
I	(*a*) Total (11)	−164.7	−129.6	+37.0	+24.7	+48.7	+29.2	+143.6
	(*b*) Average	− 15.0	− 11.8	+ 3.3	+ 2.2	+ 4.4	+ 2.7	+ 13.1
		Cod Liver Oil (Unsaponifiable Portion).						
	1	−16.0	−23.2	+ 4.4	− 2.9	+11.6	+ 5.8	+21.8
	2	−15.9	−21.6	+ 3.4	−10.2	+ 6.8	−13.7	+47.7
	3	−13.7	−17.6	− 8.8	− 8.8	+ 6.9	0.0	+45.0
	4	− 7.6	−15.8	− 9.7	− 4.8	+ 9.7	+16.5	+13.1
	5	−14.8	−33.2	+ 7.8	− 7.8	+ 7.8	+ 4.3	+32.2
	6	−12.0	− 6.3	−11.3	− 2.8	+ 7.0	+ 7.0	+19.0
	7	−13.9	− 4.2	−11.8	− 2.8	+ 4.9	+10.4	+18.1
	8	−12.9	−15.9	− 5.5	+ 0.6	+ 1.8	+ 5.5	+27.0
	9	−18.7	−17.6	− 6.6	+ 1.1	+14.3	− 6.6	+34.2
	10	−12.5	−18.7	− 2.1	− 5.4	+19.7	+ 3.6	0.0
	11	− 4.2	− 3.5	− 2.1	−15.4	+ 7.7	+13.1	+17.5
II	(*a*) Total (11)	−142.2	−177.6	−42.3	−59.2	+98.2	+45.9	+275.6
	(*b*) Average	− 12.9	− 16.1	− 3.8	− 5.4	+ 9.0	+ 4.2	+ 25.1
		Cod Liver Oil Concentrates.						
	12	−13.5	−19.8	−22.8	+ 1.6	− 5.2	+16.0	+40.2
	13	−18.1	−18.4	−25.4	+13.9	+ 0.7	+14.6	+32.6
	14	−21.0	−12.6	−17.6	+ 3.4	+ 3.5	+12.9	+31.5
	15	−15.0	−16.2	−17.3	+ 7.8	− 3.2	+35.5	+ 8.2
	16	−21.9	+34.0	−19.4	− 6.3	−13.0	+14.2	+10.6
III	(*a*) Total (5)	−89.5	−33.0	−102.5	+20.4	−17.2	+93.2	+123.1
	(*b*) Average	−17.9	− 6.6	− 20.5	+ 4.1	− 3.4	+18.6	+24.6
		Halibut Liver Oils.						
	17	−10.0	−11.7	−14.0	+ 9.8	− 4.9	+17.6	+13.4
	18	− 6.7	−11.8	−17.0	+ 1.9	− 1.0	+11.1	+23.5
	19	− 5.2	−11.5	−14.1	+ 2.5	− 2.0	+21.7	+ 8.6
	20	−14.3	−10.4	−13.0	+ 3.3	− 0.2	+ 4.6	+30.0
	21	−14.5	−22.9	− 9.1	+12.5	− 2.9	+10.4	+29.0
	22	−15.7	−10.7	−21.4	+17.3	− 7.9	+22.8	+15.8
	23	−25.2	−12.6	−11.5	+29.3	− 3.4	+ 8.0	+15.3
	24	−13.0	−17.3	−10.5	+ 9.4	− 9.0	+ 6.5	+34.0
	25	−17.1	−18.7	−10.2	+ 9.6	− 7.8	+20.5	+23.6
IV	(*a*) Total (9)	−121.7	−127.6	−120.8	+95.6	−39.1	+123.2	+193.2
	(*b*) Average	− 13.5	− 14.2	− 13.4	+10.6	− 4.3	+ 13.7	+ 21.4
		Other Fish Liver Oils.						
	26	−12.8	− 8.7	−11.6	+ 0.8	− 7.6	+ 9.6	+30.0
	27	−17.8	− 8.5	−13.5	+13.0	− 4.0	+ 1.5	+28.8
	28	−11.0	−13.5	−15.7	+ 4.6	−17.3	+32.2	+19.7
	29	−24.8	−10.8	−13.3	+ 9.8	−11.4	+14.5	+35.0
	30	−20.0	−11.9	−18.2	+26.9	− 7.9	+15.8	+14.4

	31	−21.4	−20.4	−11.9	+ 4.4	−10.3	+25.8	+33.8
V	(*a*) Total (6)	−107.8	−73.8	−84.2	+59.5	−58.5	+99.4	+161.7
	(*b*) Average	− 17.9	−12.3	−14.0	+ 9.9	− 9.8	+16.6	+27.0
		Halibut Liver Oil Concentrate.						
VI	32	−21.7	+ 0.9	−19.1	+27.0	+ 3.3	+ 8.5	− 1.0
		Cod Liver Oil Concentrate and Halibut Liver Oil Mixture.						
VII	33	−12.0	− 7.2	+ 0.5	+ 0.6	−14.3	+23.0	+ 9.9
		Sardine Body Oil.						
VIII	34	−36.0	−25.0	−37.5	− 1.6	− 9.4	+ 5.2	+103.0
IX	(*a*) Grand Total (45):	−696.3	−572.9	−368.6	+167.5	+11.7	+427.6	+1012.8
	(*b*) Average All (45):	−15.5	−12.7	− 8.2	+ 3.7	+ 0.3	+ 9.5	+22.5
		Calculated Correction Factor for Each Vitameter.						
X		1.155	1.127	1.082	0.963	0.997	0.908	0.775

TABLE VI.—VITAMETER DATA: APPLYING THE CORRECTION FACTORS—"E VALUES," A. D. M. A. LABORATORIES.

Sample.	Lab. No. 1.	Lab. No. 2.	Lab. No. 3.	Lab. No. 4.	Lab. No. 5.	Lab. No. 6.	Lab. No. 7.	Av.
				Cod Liver Oils.				
1	1.58	1.53	1.85	1.71	1.63	1.46	1.32	1.58
2	0.88	0.89	1.36	0.89	1.05	0.79	1.02	0.98
3	1.08	1.11	1.30	0.92	1.12	1.01	1.08	1.09
4	1.67	1.62	1.74	1.67	1.85	1.59	1.31	1.64
5	1.27	1.27	1.46	1.30	1.39	1.25	1.23	1.31
6	1.54	1.64	1.60	1.51	1.64	1.45	1.31	1.53
7	1.71	1.86	1.86	1.81	1.71	1.67	1.31	1.70
8	1.86	1.90	1.83	1.90	1.92	1.73	1.61	1.82
9	0.96	0.94	1.23	1.01	1.04	0.88	0.95	1.00
10	1.26	1.21	1.45	1.31	1.41	1.23	1.20	1.30
11	1.66	1.74	1.78	1.54	1.56	1.61	1.29	1.60
				Cod Liver Oil (Unsaponifiable Portion).				
1	1.34	1.20	1.56	1.25	1.54	1.32	1.30	1.36
2	0.85	0.78	0.99	0.76	0.94	0.69	1.01	0.86
3	1.01	0.95	1.01	0.89	1.09	0.93	1.15	1.00
4	1.55	1.37	1.42	1.32	1.59	1.54	1.27	1.43
5	1.13	0.85	1.34	1.02	1.24	1.09	1.18	1.12
6	1.43	1.49	1.35	1.31	1.51	1.37	1.30	1.39
7	1.43	1.55	1.37	1.34	1.51	1.44	1.32	1.42
8	1.65	1.55	1.68	1.58	1.67	1.57	1.61	1.62
9	0.85	0.87	0.92	0.88	1.04	0.77	0.95	0.90
10	1.13	1.02	0.96	1.02	1.34	1.05	1.18	1.10
11	1.58	1.55	1.51	1.16	1.54	1.45	1.30	1.44
				Cod Liver Oil Concentrates.				
12	27.7	25.0	23.2	27.1	26.3	29.2	31.0	27.0
13	21.4	20.8	18.3	24.8	22.8	23.5	23.3	22.1
14	21.2	22.9	20.6	23.0	24.0	23.7	23.6	22.7
15	74.5	71.5	67.9	78.5	73.4	93.2	63.6	74.6
16	18.7	32.1	17.9	18.8	18.1	21.6	17.8	20.7

				Halibut Liver Oils.				
17	41.0	39.4	36.8	41.7	37.6	42.0	34.7	39.0
18	37.1	34.3	30.9	33.7	34.1	34.7	33.0	34.0
19	20.4	18.6	17.3	18.4	18.3	20.5	15.8	18.5
20	57.0	58.3	54.1	57.2	57.6	54.7	58.3	56.7
21	76.4	67.5	76.1	83.8	73.3	77.5	77.6	76.0
22	18.1	18.7	15.8	21.0	17.1	20.7	16.7	18.3
23	27.8	31.7	30.6	39.8	31.0	31.5	28.8	31.6
24	50.7	47.1	48.7	53.0	45.9	48.6	53.5	49.6
25	62.0	59.5	62.8	68.0	59.7	70.7	62.1	63.6
				Other Fish Liver Oils.				
26	101.0	103.0	95.5	96.7	92.4	99.3	100.8	98.5
27	56.0	60.8	55.2	64.2	56.7	54.4	59.0	58.0
28	88.8	84.1	78.9	86.7	72.5	103.7	80.2	85.0
29	37.4	42.8	39.8	45.0	37.8	44.3	44.5	41.7
30	62.0	66.6	59.3	81.8	61.9	70.6	60.0	65.8
31	40.7	40.2	42.6	45.0	40.3	51.2	46.5	43.8
				Halibut Liver Oil Concentrate.				
32	649.0	815.0	607.0	875.0	742.0	707.0	562.0	708.0
				Cod Liver Oil Concentrate and Halibut Liver Oil Mixture.				
33	39.3	41.0	42.5	37.8	33.6	44.9	33.3	38.9
				Sardine Body Oil.				
34	0.47	0.54	0.43	0.61	0.58	0.6	1.0	0.6

DISCUSSION.

Inspection of Table I will reveal that the respective "E values," obtained by Vitameter, for the seven laboratories on the eleven cod liver oils varied materially. However, there was fairly good agreement between the results obtained by some of the laboratories. For instance, Laboratories 1 and 2 checked rather closely and the results reported by Laboratories 5 and 6 were in good agreement between themselves but much higher than the other two. The greatest difference between the maximum and minimum results was for Sample No. 2 the maximum value, 1.31, being 72% larger than the minimum value, 0.76. The best agreement in this series was for Cod Liver Oil No. 11. The maximum value, 1.79, was 23% larger than the minimum value, 1.44. The results obtained for sample No. 11 are of particular interest since this sample was the official U. S. P. Standard of Reference Cod Liver Oil. The average "E value," 1.61, for the U. S. P. Standard of Reference Cod Liver Oil is somewhat lower than the "E value," 1.74, reported by Morgan (5).

It will be noted that the "E values" determined on the unsaponifiable portion of the Cod Liver Oils are lower than those reported for the fluid oils except in the case of Laboratory No. 7. The values reported for the assays of the unsaponifiable portion of the Cod Liver Oils are not only lower but more variable than for the fluid oils. The greatest difference in this series is for Sample No. 5 for which the maximum value, 1.52, is 100% greater than the minimum value, 0.75. The smallest difference between the maximum and minimum value is for Sample 6 the maximum value, 1.68, being 35% larger than the minimum value, 1.24. These greater variations would seem to indicate that the cause lies in errors due to the separation of

the unsaponifiable portion of the oil. The average "E value," 1.45, for the unsaponifiable portion of the U. S. P. Standard of Reference Cod Liver Oil is lower than the "E value," 1.58, reported for similar determinations by Morgan (5).

Five samples, No. 12 to No. 16, of cod liver oil concentrates were assayed for their Vitamin A content. These samples were assumed to be typical of cod liver oil concentrates in general. Here it is also apparent that there is a grouping of data according to instrument, Laboratories 1, 2 and 3 having lower values while Laboratories 6 and 7 were highest. The greatest difference between the maximum and minimum values reported for the cod liver oil concentrates was for Sample No. 12 (Laboratory 7) for which the maximum value, 40.0, is 87% larger than the minimum value, 21.4 (Laboratory 3). The least difference between the results reported by the different laboratories was for Sample No. 16, the maximum value, 23.76, (Laboratory 6) is 46% greater than the minimum value, 16.25 (Laboratory 1).

The greatest deviation in the "E values" of the halibut liver oils was for Sample No. 23 in which the maximum value, 41.50 (Laboratory 4) is 73% greater than the minimum value, 24.03 (Laboratory 1). The least deviation in the halibut liver oil series was for Sample No. 17 for which the maximum value, 46.46 (Laboratory 6) is 37% larger than the minimum value, 34.0 (Laboratory 3). In selecting the halibut liver oils an attempt was made to secure samples possessing a considerable range of Vitamin A potency. This was apparently accomplished since the average "E values" varied from 18.57 to 77.52 which indicates that the Vitamin A potency of Sample No. 21 is over four times that of Samples No. 22 and No. 19.

In the next series, "other fish liver oils," the greatest deviation was for Sample No. 29 for which the maximum value, 57.5 (Laboratory 7) was 77% greater than the minimum value, 32.54 (Laboratory 1). The least deviation for this series was for Sample No. 30 for which the maximum value, 77.70 (Laboratory 6) was 45% greater than the minimum value, 53.68 (Laboratory 1). Again, for the Halibut Liver Oil Concentrate No. 32 there is a wide variation in the results. Laboratories 1 and 3 had the lowest value with Laboratory 4 running highest, and the other four agreeing quite closely. Finally, in the case of Sample No. 34, Sardine Body Oil, this oil had the lowest Vitamin A content of any. Comparing these results, we again find that they group themselves according to certain instruments with Nos. 1, 2 and 3 having the lowest "E values" and 6 and 7 the highest.

From the data in Table I, regardless of the nature of the product, in general one fact appears to stand out as far as Vitamin equipment is concerned, namely:

Comparing the data for the different laboratories for the same respective samples the variations are of such a magnitude and order, that they indicate the fluctuations are due mainly to inherent factors in the instrument, and perhaps to some extent to the particular laboratory technique. That is to say, regardless of the above fluctuations, the data indicate that the Vitameter is capable of quantitatively measuring Vitamin A for any one laboratory at a level, however, which should be readjusted to some standard.

The Vitameter assay results in Table II reported by coöperating laboratories are more limited and do not permit of the same comparison as for the results reported by the A. D. M. A. Laboratories. It will be noted (comparing Laboratories 8, 9, 10 and 11) that the average values reported for all these coöperating laboratories are consistently lower for practically all the thirty-four samples than the average

values for the seven A. D. M. A. laboratories. These lower averages are due principally to the data reported by Laboratory No. 8. Again interest in this series of results is perhaps principally centered in Sample No. 11—the U. S. P. Standard of Reference Cod Liver Oil. Laboratories 10 and 11 agree fairly well with the A. D. M. A. results. The average "E value" obtained by the four laboratories was 1.28 which is much lower than the "E value," 1.61, obtained by the seven A. D. M. A. laboratories. The impression gained here is that the same general effect is evidenced as with the instruments used by the A. D. M. A. Group, namely, a consistent trend to run in groups.

The values reported by Laboratory No. 12 are of particular interest since, as stated previously, they were obtained with a Hilger Vitameter which had been modified by replacing the copper arc with a General Electric S-1 Therapeutic Lamp. This was not done necessarily with the expectation that the values would agree with the corresponding data where the copper arc was used, but rather with the possible thought that the same relationship would exist between the different oils and some set standard. Inspection of the results for Laboratory No. 12 show that the "E values" are decidedly less than the corresponding data for any of the other eleven laboratories. That is, they were of a lower magnitude. Furthermore, comparing the variations between different oils, it would seem that the results for Laboratory 12 do not follow the same direction as those for the standard instrument. These results would seem, therefore, to indicate that the modified Vitameter gives values which are entirely different. For this reason the data were not averaged with those from the other four laboratories. Correspondence with the manufacturers of the Vitameter and the G. E. S-1 Therapeutic Lamp elicited from each a statement that Vitamin A assays could not be made with a Vitameter in which the copper arc was replaced by the ultraviolet lamp in question.

In its report, Laboratory No. 9 stated,

> "We found that the results obtained with the spectrophotometer were much more reliable than those obtained with our old Vitameter. In this connection attention should be called to the rather rapid deterioration of the Vitameter with use. This is particularly true of the silver film which is attached to the quartz plate to transmit the radiations near 3280 Angstrom units. This type of change tends to cause the Vitameter to produce other than strictly monochromatic light which in turn produces an inaccuracy in the 'E values,' for the logarithm of absorption is proportional to the concentration only for monochromatic light."

Fortunately, five laboratories were equipped with high-precision spectrophotometers. One, however, was able to complete only the assays on the series of cod liver oils. The results from those five laboratories are given in Table III together with the average of the Vitameter data for the A. D. M. A. Committee. The variation in the data on the liquid cod liver oils was greatest for Sample No. 5 of which the maximum value, 1.31 (Laboratory No. 3), is 64% greater than the minimum value, 0.80 (Laboratory No. 14). The least variation in the results reported by the five laboratories was for Sample No. 10 of which the maximum value, 1.30 (Laboratory No. 14), is 16% greater than the minimum value, 1.12 (Laboratory No. 13). The average "E value" obtained in the spectrophotometer assays of the U. S. P. Standard of Reference Cod Liver Oil was 1.46. This value is about 90% of 1.61, obtained by the A. D. M. A. Laboratories and over 114% of 1.28, reported by the coöperating laboratories for their Vitameter assays.

Four laboratories reported results of spectrophotometer assays of the unsaponifiable portion of the cod liver oil samples. In this series the greatest deviation was for Sample No. 1 of which the maximum value, 1.43 (Laboratory No. 3) is 99%, larger than the minimum value, 0.72 (Laboratory No. 9). The least deviation in this series was for Sample No. 7 of which the maximum value, 1.35 (Laboratory No. 3), was 5% greater than the minimum value, 1.29 (Laboratory No. 13). The "E value" for the unsaponifiable portion of the U. S. P. Standard of Reference Cod Liver Oil was 1.22 as compared with 1.45 obtained by the A. D. M. A. Laboratories on the Vitameter.

Four laboratories reported spectrophotometer assays for the cod liver oil concentrates. Of this series the greatest deviation in the results was for Sample No. 13 of which the maximum value, 20.10, was 25% greater than the minimum value, 16.13. The least deviation was for Sample No. 15 of which the maximum value, 67.41, was 8% greater than the minimum value, 62.40.

Referring to the results for the halibut liver oil series, the greatest deviation between the four different laboratories was for Samples No. 17 and No. 24, the maximum value reported for each of these being 29% larger than the minimum value. The least deviation was for Sample No. 19 of which the maximum value, 16.95, was only 9% greater than the minimum value, 15.50. Here also the average vitameter data for the corresponding 9 halibut liver oils ran definitely higher than those for the spectrophotometer.

In the case of the spectrophotometer assays of the 6 "other fish liver oils," the greatest deviation in this group was for Sample No. 30 of which the maximum value, 59.80 (Laboratory 9), is 18% greater than the minimum value, 50.79 (Laboratory 3). The least deviation in this series was for Samples No. 28 and No. 29, the maximum values reported for both of these samples were only 6% greater than the minimum values. Here again the Vitameter data for the corresponding oils ran appreciably higher than those for the spectrophotometer.

It is obviously of interest to compare the results obtained with the Vitameter and spectrophotometer under comparable conditions in the same laboratory. Three laboratories (Table IV) made such comparable assays. The average "E values" obtained with the Vitameter in the cod liver oil series are somewhat larger than the average results obtained with the spectrophotometer. However, the Vitameter results obtained by Laboratory No. 3 are higher than those obtained with the spectrophotometer for only five of the eleven cod liver oils. With two exceptions the results reported by Laboratories Nos. 9 and 10 for cod liver oils were uniformly higher for the Vitameter than with the spectrophotometer.

The spectrophotometer "E values" were lower for the unsaponifiable portion of the cod liver oil samples than for the liquid oils. However, the same general trends between the various oils occurred in the former as in the latter series.

The average Vitameter "E values" of the five cod liver oil concentrates were higher than those of the spectrophotometer for Samples No. 12 and No. 16, but the results obtained with the spectrophotometer were on the other hand larger than the Vitameter results for Samples Nos. 13, 14 and 15. The cause of this inconsistency is not known.

In the case of the Halibut Liver Oils the average of the Vitameter "E values" reported by the four laboratories is consistently greater than the average spectro-

photometer "E values" reported from the same laboratories. However, inspection of the results of the individual samples shows that the variations in the Vitameter results were greater than the spectrophotometer results.

To sum up, the general impression from the data, in Tables III and IV, is that comparing corresponding individual samples the Vitameter gives values that run higher than those with the spectrophotometer, irrespective of the type of product under test. On the other hand, it would seem in assaying the same oils (or concentrates) by the different spectrophotometers that the values showed a much wider variance than one would have expected or predicted. The fault would hardly seem to lie in the lack of uniformity of the samples sent out since all precautions were taken to avoid this. There is a tendency for certain samples to react peculiarly and this makes it difficult to evaluate them as precisely as desired. This happens with both the Vitameter and the spectrophotometer. There are instances on the other hand where the data for the same oils are in very close agreement when obtained by one type of instrument and at wide variance when determined with the other instrument. In general, the Vitameter results, as stated previously, show a definite indication of falling into groups.

Since the principal interest in this study was concerned with the possible practical usefulness of the Vitameter for making Vitamin A assays of cod liver oil and related products, a statistical study has been made of the results obtained with the Vitameter. Since a survey of the data revealed that there were probably fewer variables in the assay procedures of the seven A. D. M. A. Vitamin Committee Laboratories than in those of coöperating laboratories, it was decided to confine the statistical analyses to the data in Table I.

On comparing the values for each laboratory with the average for the seven, it will be seen that the data for individual laboratories tend to vary in a definite direction. For instance, in the case of Laboratories Nos. 1 and 2, their results are definitely below the average, while those for No. 7 are decidedly above the average. The values for the other 4 laboratories fall in between. In Table V, the data have been calculated to bring out this tendency more clearly by expression as plus or minus the per cent of deviation from the average. The results for the liquid cod liver oils show that the Vitameters for Laboratories Nos. 1, 2 and 7 gave distinctly different values than those for Laboratories Nos. 3, 4, 5 and 6. The averages for the eleven samples (Line Ib) for the respective laboratories are, −15.0, −11.8, +3.3, +2.2, +4.4, +2.7 and +13.1. If one compares the data for the other samples, non-saponifiable fraction, cod liver oil concentrates, halibut liver oils, etc., it is seen that each instrument has, within limits, a tendency to give a characteristic deviation. To obtain the most representative and fairest cross-section picture of this for each Vitameter when used under conditions as laid down here, one should consider the averages of all 45 samples as given in Line IXb. These data indicate pretty accurately how far below, or above, the average the true values lie. In other words, with these data it is suggested that each one apply a correction factor to his particular equipment and in this way bring his values more in line with the others. To illustrate, Table V, line X, Laboratory No. 1, the proposed factor is 1.155 and for Laboratory No. 7 it is 0.775.

The results in Table I have been recalculated by applying these respective factors. These recalculated results are given in Table VI. A careful comparison of

the corresponding values in the two tables shows that the variations have been smoothed out to a considerable degree, especially for the more potent oils. There are still some gross exceptions which would seem to be due to possible errors in making a thorough mixing of the dilutions, to contamination of the cell walls with oil film, or to other factors which are not obvious or easily detected.

This method of calculation would seem to show that the Vitameter in order to be capable of measuring vitamin A most accurately, for comparative purposes, should be checked or standardized against some oil or group of oils which have been carefully read on a standard spectrophotometer and preferably bio-assayed against a standard or suitable sub-standard oil, and also read on standard spectrophotometer.

The most logical oil to use for this purpose is the U. S. P. Reference Cod Liver Oil which has an assigned biological value of 3000 units per Gm. For a more satisfactory standardization of the Vitameter, it might be more feasible to use a high potency oil, like halibut liver oil, which had been biologically evaluated against the U. S. P. Reference Oil. The procedure would then call for each laboratory to determine its own "E value" of the standard oil and from this calculate its own conversion U. S. P. units per Gm. factor. In practice even a standard spectrophotometer should be calibrated by this procedure.

SUMMARY AND CONCLUSIONS.

The data from the various laboratories show that individual laboratories can obtain consistent results, and that the results of different laboratories bear a fairly constant relation to those of other laboratories.

It is quite apparent from the results of this study that in order to correlate the data of different laboratories it is essential to refer the data of all laboratories to a standard of reference. The U. S. P. Standard of Reference Cod Liver Oil, which is being widely used for biological assays, is well suited to this need. The average "E value" obtained for this oil by the Vitamin Committee was 1.61.

The Vitamin A potency of the U. S. P. Standard of Reference Cod Liver Oil has been officially designated as 3000 Vitamin A units per Gm. Hence, the tentative factor for converting Vitameter E values into U. S. P. XI Vitamin A units per Gm. is 1875.

It is apparent from the statistical discussion of the data obtained in this study, that in conducting Vitamin A assays each laboratory must apply a factor for converting its "E values" into U. S. P. Standard of Reference Cod Liver Oil biological Vitamin A units.

In practical operation the Vitamin A potency of a cod liver oil may be computed in terms of U. S. P. XI units per Gm. from the Vitameter "E value" by

$$\frac{1.61 \text{ times } 1875 \text{ times "E value" of oil being assayed}}{X}$$

where X = the "E value" obtained by the individual laboratory for the U. S. P. Standard of Reference Cod Liver Oil.

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ASSAY OF THE N. F. PEPSIN PREPARATIONS.*

R. K. SNYDER, LOUIS GOLDBERG AND E. N. GATHERCOAL.

Elixir of Pepsin N. F. V and N. F. VI, Elixir of Pepsin and Rennin N. F. V and N. F. VI, Compound Elixir of Pepsin N. F. VI and Glycerite of Pepsin N. F. VI were made up and each preparation was divided into three parts and placed in Pyrex bottles for storage. One bottle of each was kept on an open shelf, one in a dark cupboard and one in a refrigerator.

The proteolytic activity of each at the end of a year was determined. The average results are as follows:

Elixir of Pepsin N. F. VI,	175 per cent
Elixir of Pepsin N. F. V,	60 per cent
Elixir of Pepsin and Rennin N. F. VI,	162 per cent
Elixir of Pepsin and Rennin N. F. V,	140 per cent
Compound Elixir of Pepsin N. F. VI,	175 per cent
Glycerite of Pepsin N. F. VI,	112 per cent

It should be remembered when inspecting the table that all of the preparations except the glycerite were made up to the N. F. formulas, that is, 200 per cent strength, and are up to the official standards as long as they are above 100 per cent strength. The glycerite was made up to 114 per cent strength and is up to standard as long as it is above 100 per cent strength.

As would be expected, the preparations kept in the refrigerator held their activity the best, those in the dark cupboard next and those on the shelf the least. However, the differences between the three are very small and do not warrant the extra care in storage.

It will be observed from the table that the N. F. VI preparations maintained a higher level of proteolytic activity than the N. F. V. This is particularly noticeable in the Elixir of Pepsin. This is due to the fact that the N. F. VI product has a higher hydrogen-ion concentration (slightly over p_H 4) than the N. F. V (about p_H 2.5), and is buffered. The difference in proteolytic activity due to this change in p_H is of a much larger order than that due to storage conditions and indicates that the proper p_H of the solution is of vital importance.

In connection with these assays of the N. F. pepsin preparations, certain refinements in the official assay process (see N. F. VI page 119) were tried out and seemed to be real improvements. These refinements may be briefly mentioned as follows:

(*a*) The amount of dilution of the Elixir was changed from "5 cc. of Elixir to 145 cc. of this dilute acid" to "3.33 cc. of Elixir to make 100 cc. with this dilute acid." It was found that a more accurate dilution could be prepared by using a pipette carefully calibrated to deliver 3.33 cc. and a 100-cc. volumetric flask.

(*b*) The solution of Reference Pepsin is likewise prepared in volumetric glassware to insure greater accuracy.

(*c*) A sufficient quantity of the egg albumin is prepared at one time for the

* National Formulary Research Project F 3 in progress in the N. F. Laboratory, Chicago, Illinois.

assays of the day and kept in a well-stoppered container. The coagulated albumin passed through the sieve is well mixed, so that a uniformity is attained even if there be a variation in the albumin of different eggs.

(*d*) The granulated albumin is reduced in a mortar with some of the dilute acid to a uniform suspension and then quantitatively transferred to the digestion bottle. This insures a more uniform final precipitate and apparently does not influence the amount of albumin digested.

(*e*) The period of "standing" to permit complete and uniform precipitation is increased from "30 minutes" to "over night." This may appear as a very marked increase, yet it has been found that the "reading" of the precipitates is much improved and apparently no "errors" are developed by the increased time of standing.

(*f*) Finally, the whole set-up of six standards graduated in steps of 0.5 cc. of the dilution of standard pepsin (equivalent to less than 0.0003 Gm. of pepsin per "step") and the two tubes of "unknown" of different strengths, permits a close comparison of the precipitates in the tubes of the "unknown" with that in the tubes of the standard. If the reading of the "unknown" should not be exactly equivalent to that of one of the standards, but falls in between two of them, the value may be interpolated.

The detailed assay process as used in this work is as follows:

Mix 35 cc. of normal hydrochloric acid with 385 cc. of distilled water. Dilute exactly 3.33 cc. of Elixir of Pepsin to 100 cc. with this dilute acid in a 100-cc. volumetric flask. Dissolve 0.1458 Gm. of Reference Pepsin (see U. S. Pharmacopœia XI, page 486) in 250 cc. of this acid. Immerse a sufficient number of eggs in boiling water for 15 minutes to provide sufficient coagulated albumin for the assays of the day. Remove the eggs and when they have sufficiently cooled to handle, remove the shell, pellicle and all of the yolk, and at once rub the albumin through a clean, dry, hair or brass, No. 40 sieve, rejecting the first portion that passes through the sieve and keeping the remainder in a stoppered container. Place a 10-Gm. portion of the granulated egg albumin in a porcelain mortar with 10 cc. of the dilute acid and rub until the albumin is completely suspended. Quantitatively transfer this suspension to a wide-mouthed bottle of about 100 cc. capacity using 20 cc. of the dilute acid to rinse the mortar. Repeat this procedure until a sufficient number of bottles have been prepared. Place them in a water-bath warmed to 52° C. To one bottle add exactly 3 cc. of acidulated solution of Elixir of Pepsin and 7 cc. of the dilute acid. To a second bottle add exactly 5 cc. of the acidulated solution of Elixir of Pepsin and 5 cc. of the dilute acid. Prepare a set of standards in a similar manner to the above using exactly 4.0 cc., 4.5 cc., 5.0 cc., 5.5 cc., 6.0 cc. and 6.5 cc. of the acidulated solution of Reference Pepsin, and in each case a sufficient amount of the dilute acid to bring the total liquid to a volume of 40 cc. At once cork the bottles securely with smooth cork stoppers, invert them three times, and place in a bath adjusted to maintain a temperature at 52° C. Keep the bottles at this temperature for two and one-half hours, agitating the contents equally every 10 minutes by inverting the bottles once, making sure that no particles of albumin adhere to the stopper or walls of the bottle. Remove the bottles from the bath; pour the contents of each into conically shaped measuring vessels of suitable capacity having a diameter not exceeding 1 cm. at the bottom, and graduated from the tip to the 1.0-cc. mark in 0.05-cc. divisions and from the 1.0-cc. to the 5.0-cc. mark in 0.1-cc. divisions. All of the measuring vessels must have the same internal taper. Transfer the undigested egg albumin which adheres to the sides of the bottles to the respective measuring vessels with the aid of small portions (about 15 cc. at a time) of distilled water until the total amounts measure 50 cc. each. Stir the mixtures well, and allow to stand over night. Keep the measuring vessels in a perfectly vertical position during the sedimentation time. Compare the tubes containing the Elixir of Pepsin with the tubes containing the Standard Reference Pepsin and observe which tubes have approximately the same amount of undigested egg albumin. Calculate the percentage of active pepsin in the Elixir of Pepsin. If neither the 3-cc. nor the 4-cc. samples of the acidulated solution of Elixir of Pepsin produce amounts of undigested egg albumin which fall within the range of the set of

standards, it is then necessary to use either less or more of Elixir of Pepsin as the case may be until the amount of albumin falls within the range of the standards.

The following is a sample of the calculations used:

If it is found that 3 cc. of the acidulated solution of Elixir of Pepsin is equal to 5 cc. of the acidulated solution of Reference Pepsin, the calculations would be as follows:

One cc. of the acidulated solution of Reference Pepsin contains 0.000583 Gm. of Pepsin, therefore, the amount of Pepsin in the 3 cc. is equal to 0.000538 × 5 or 0.002915 Gm. Therefore, the amount of pepsin in 100 cc. of an Elixir of Pepsin of this strength would contain 1000 times as much pepsin or 2.915 Gm. Dividing this amount of pepsin by 1.75 Gm. (the standard required in the Elixir of Pepsin) gives the percentage as used in the above table of figures.

THROUGH THE APOTHECARY TO THE MEDICAL INTERN.

BY ROLAND T. LAKEY.*

The evidence of our changing professional attitudes and viewpoints is embodied in the records of our state association's annual convention programs. A comparison of the papers and discussions of 10, 20, 30, 40 or 50 years ago will reveal a gradual waning of interest in the professional side of retail pharmacy and a corresponding increase of interest in the commercial development of the drug store. It is not my intention to add to the often repeated expression of regret that this has taken place, but rather to point out that we still have only one ground upon which our extremely diversified experiences can make contacts for the purpose of professional improvement, namely, our common interest in the arts and sciences of pharmacy. Due to the failure of our state associations in maintaining this interest, we must seek other agencies for promoting a professional consciousness. The AMERICAN PHARMACEUTICAL ASSOCIATION, of course, provides for this nationally, but has been unsuccessful thus far in enlisting sufficient numbers to make much of an impression locally. It is true that the branch programs are mainly educational and professional in character, but they are not systematically arranged and do not consistently provide for attaining a definite objective. The mixed character of the membership is another reason why they cannot confine their programs to professional subjects. There is in each metropolitan center, however, a number of registered pharmacists whose interests are wholly professional; I refer to the hospital and professional pharmacy apothecaries. With this thought in mind last May, the writer sent invitations to all of the hospitals, professional pharmacies and other institutions conducting an exclusive compounding and dispensing service in the Detroit district, to meet at the Receiving Hospital for the purpose of organizing a Section of Apothecaries of the Detroit Branch of the A. PH. A. Twenty-seven attended the meeting. These men and women welcomed the suggestion of an organization of their own and proceeded to elect officers. R. L. McCabe, proprietor of a professional pharmacy, was chosen as *President*. James Early, chief pharmacist of the Detroit Receiving Hospital, was elected *Secretary* and Helen Linsky, chief pharmacist, St. Joseph Hospital, *Treasurer*. It is estimated that there are about 100 eligible for membership in the metropolitan area and it is expected that practically all will be enlisted when the fall season starts.

* Section on Education and Legislation, A. PH. A., Dallas meeting, 1936.

After the organization was completed, a discussion followed as to the selection of some worth-while project to engage in. Mr. McCabe solved the problem by suggesting that, through their contacts with interns and staff physicians, the hospital apothecaries could render unusual services in behalf of professional pharmacy. It was decided that a systematic campaign of education in the new U. S. P. and N. F. was the most expedient plan to pursue, so plans were formulated for an organized and consistent series of lectures and demonstrations, to be conducted uniformly at the various institutions from October to June. There are over fifty hospitals in the district and we hope to contact the medical staff of each.

Another project to be worked upon is a hospital formulary to meet the needs of the district. Committees will organize the lectures and demonstrations and they will be presented by competent speakers.

My only excuse in bringing this premature local plan to your notice is to call attention to its potentialities at this particular time when the old and new graduates of medicine will be more receptive to U. S. P. and N. F. information and advice relative to the official materia medica. We feel confident that if other metropolitan A. PH. A. branches will organize sub-sections and put into effect similar plans the accumulated results will help to develop a certain amount of professional interest.

A NEW STUDY OF PRESCRIPTION PRICING.*

BY JOSEPH H. GOODNESS.[1]

About eighteen years ago I was introduced to the mysteries of a drug store. During the first day the proprietor invited me to watch how a prescription was filled. With running comment on the meanings of the strange drachm and ounce curlicues, abbreviated Latin titles and directions in hieroglyphics, he completed the prescription, acknowledged my "Ah!" and retired to the desk to number, label and price the finished work. I watched him closely from a distance. With the labeling completed, he dipped his pen and scratched a "65" upon the blank. The ink failed to deposit; he tried again, and again failed to leave a mark. For his third try he once more dipped his pen and this time marked the prescription "75." The price was final.

Although untrained in business methods I could not help doubting the honesty of my benefactor and teacher. Longer contact corrected the first impression, for my friend proved to be of the finest ethical and social character, but the feeling of uneasiness the incident created has always remained a stimulus that has led to an extensive study of the subject.

This study has disclosed many things, among them the following: *First*, most druggists do not use a recognized or definite system of prescription pricing, for as scientists they revolt against other people's price-lists, yet cannot figure out a better system of their own. They have in many cases become scientists who guess at prescription prices.

Second, many druggists using a system frequently change from one to another.

Third, all pricing systems have an economic rather than a professional or psychological basis—that is, the final price is the result of several individual costs, each assigned to some particular material or service involved in filling the prescription.

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* Based upon a paper presented before the Section on Commercial Interests, A. PH. A., Dallas, Texas, 1936. The original paper has been published in the January 1937, issue of the *Pacific Drug Review*.

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This is unlike the charge made by doctors, dentists and other professional men, whose charges are somewhat standard, with a final price usually a multiple of whole or half dollars. Pharmacists, slaves to custom as are most humans, have never wholeheartedly tried to charge a professional price in place of an economic one. The few pharmacists who have sought to establish the practice of a single price for all prescriptions have been motivated by the wrong ideas, for they have failed either because they neglected to set the price high enough, and thus caused their working capital to vanish through the loop hole of "operating expenses," or the law (semi-judicially) stopped the "prescription insurance" (a year's supply of prescriptions for $10.00) because the operators had no license to practice the calling of insurance. In any event, pharmacists have made their bed and must continue to calculate prescription prices upon an economic basis.

Fourth, most systems in use yield fair-to-excellent prices for the localities in which they are used, but the component charges constituting the price cannot be explained in a manner that will enable the pharmacist to stand his ground when a customer questions the fairness of the price. As a result many pharmacists using any of the existing systems reduce the prices of their prescriptions below the system's figures.

A study of the field discovers what appear to be three basic systems, and all systems now in use seem to be either modifications of these three, or merely arbitrary price-lists. The first basic system has a single formula for all prescriptions: *Cost of materials doubled, plus an additional charge.* The additional charge is sometimes explained as a labor charge; at other times as a combined charge for labor and one or more other charges. The second basic system, also for all prescriptions, has this formula: *Materials at selling price, plus a compounding fee, plus a service charge* (based upon the number of doses or applications in the prescription). This system really has four formulas, for prescriptions are divided into four classes, and the above three charges are given different values for each class. The third basic system is a combination of *minimum price-lists* (for inexpensive-material prescriptions), *and formulas* (for the more-expensive-material prescriptions). This system divides prescriptions into two classes: those compounded, and those ready-made.

Representative pricing systems are those of Evans, *Pacific Drug Review*, Blanner, Finneran, Seltzer, Secord, and the South Dakota Pharmaceutical Association.

The criticism to be made of existing systems is *not* that they yield inequitable prices, but that they are insufficiently explained, or, where explained, that the explanation is arbitrary or unscientific, either because charges of a variable and a fixed nature are combined, or because some charges are entirely omitted and others are exaggerated to compensate for the omissions. If a pharmacist has no justifiable grounds for asking a price, or feels that the charges are excessive, prices come down. Another criticism is of the constantly present *series of exceptions* to the general rule or formula. In fact, often the exceptions cover as many cases as the rule does itself.

Because of these faults there is need of a formula for pricing prescriptions so fundamental in its elements and accurate in principle that it could be applied to any store, anywhere, after slight modification in its values to fit local conditions. A formula of this sort is not easy to find, and it is possible that the one to be presented falls short of the mark, but it is nevertheless offered as one that aims at this

goal. Its value, I believe, lies in the fact that each charge going into the final price is so explained that any druggist can find unlimited support for it in economics, business, and law, and that no charges are omitted. If this system can convince even a small number of druggists that prescription prices should not be based upon factors other than costs and competition, the time spent in creating it will be considered well spent.

Before presenting the pricing system, it might be well to outline the principles upon which it has been constructed. If the reader won't agree with the principles, then he can and probably will find cause to disagree with much that follows in the explanation of the system. The principles follow. (As you read each principle check it if you can agree:)

1. Each department in a drug store most, in the long run, support itself. The prescription department, in particular, should not be an exception to this rule.
2. The pharmacist must get, as part of the price, the cost of *materials used* in the prescription (ingredients, label and container).
3. For each prescription filled, the druggist is entitled to add a reasonable *merchantman's profit* to the material cost.
4. All true economic *expenses* of a department (in addition to material cost) must be paid by customers of that department. In other words, prescription department expenses must come out of prescription sales. (The word "economic" as used here outlaws all needless or unreasonable expenditures in the department.)
5. The pharmacist is entitled by legal and economic laws to charge for the exercise of his *skill and labor* in filling a prescription. Neither Pharmacy nor the law makes demand upon the members of the profession to serve others consistently without making this charge.
6. The pharmacist should charge for the *legal risks and duties* that the law places upon him every time he fills a prescription.
7. Rarely (probably one in five hundred or a thousand) the druggist, in his duty to create confidence in the prescription, must charge an *additional amount* over those charges already enumerated.
8. The system must be easy and simple to manipulate (although the system itself need not be simple), and the price for each prescription should be figured by arithmetical rather than algebraic means.
9. The system should provide the means for pricing *all* prescriptions.
10. The system should not be arbitrary, but must be applicable at all times and places, under all possible economic conditions, after but slight adjustment.

From an examination of these principles it can be seen that a pharmacist should make charges for each prescription as follows: (1) the material cost, (2) the merchantman's profit, (3) a fixed part of the department's overhead expenses, (4) a charge for labor and skill, (5) a charge for the legal liabilities and duties imposed by law and sometimes (6) an additional, psychic, charge. These charges are not duplicated in whole or in part; therefore they should all be present in our system. The system under discussion makes use of six charges, but has provision for reducing the number to five under certain conditions.

The absolute need of each of these charges as separate values requires an explanation. These charges are of two types: those that vary greatly from prescription to prescription (called the *variable* costs), and those that remain constant for each prescription (called the *fixed* costs). As examples of the variable costs we have the material cost, the profit, the labor charge and the liability charge. The psychic charge may also be placed in this class when it is used. Each variable charge must

be figured separately for each prescription filled. This statement may discourage the average pharmacist who probably visualizes, at this point, a battery of accountants calculating the price of a two-ounce cough syrup. To ease his mind, let me explain that only the material charge has to be figured "from scratch" after the system is established, for all other variable charges, except the psychic charge, can be found on charts by the simple method of sliding the finger along the line assigned to the *type* of prescription to the column that corresponds to the *quantity* involved. The charge is beneath the finger tip.

The other class is the fixed charge. The overhead charge is the only fixed charge in the system. This is figured once a year, or whenever economic conditions change so much that a wholesale readjustment of the system is necessary.

Because economic conditions differ in various parts of the United States, and also because there is not yet a sufficient amount of information collected concerning price levels in the different sections of the country as well as other necessary figures, the system is presented in outline form only. The rules for the collection and arrangement of figures for the various charts of charges are provided, so that any pharmaceutical organization, commercial pharmacy teacher, or individual pharmacist may make a working system for prescription pricing in his locality. A discussion of each charge with rules follows.

I. The Cost-of-Materials Charge.—This charge should cover the following items: (1) cost of ingredients used, (2) cost of the container used, (3) cost of the label and (4) any special costs assignable to a particular prescription, as cost of heat for sterilization, cost of filter paper, etc. The cost of ingredients should be determined with the aid of the following rules: (1) Goods should be marked as soon as received, with the cost of the entire amount purchased and the cost of every commonly used unit. As an example, aspirin purchased in a pound container should be marked with the price of the pound, the ounce and the drachm. Codeine, on the other hand, should be marked down to the cost per grain. (2) Prices should be list. Discounts received should not be handed down to the customer. (3) The cost of each unit should be expressed in whole cent amounts. (4) Materials entering any prescription should not be below a set minimum charge (of, say, five cents). This material charge can be combined with the profit amount, which is next discussed.

II. The Profit Charge.—All vendors are entitled to a reasonable profit upon cost of materials furnished. This charge can be figured by marking up the material cost by any given percentage, depending upon the profit desired. Since economic conditions change, it may be a good policy to add this charge separately to every price figured. A business may, however, combine the cost and the profit, and then mark the package received accordingly. Either one or the other method must be used. To mix them would cause confusion. It is worth noticing that in the entire system this is the only *profit* charge. All other charges are true costs or expenses.

III. The Overhead Charge.—The patrons of the prescription department must eventually pay for all necessary expenses to keep the department open. These expenses are divided into two classes: those that are like the expenses that customers in any other department pay (called the *General Overhead* expenses), and those that are due solely to prescription work (called the *Prescription Department Overhead* expenses). Each class should be figured separately about once a year and

the results combined into a single figure to be added to the price of every prescription filled.

The *General Overhead* is figured by finding the annual expenditure for general upkeep and operation of the entire store, and then apportioning this expense to the departments upon some equitable basis. The items of general overhead should consist of *at least* the following:

1. Rent
2. Repairs
3. Delivery
4. Losses from bad accounts
5. Depreciation of fixtures
6. Insurance expenses (fire, public liability, plate glass, etc.)
7. Interest on borrowings and investment
8. Taxes (property, income, sales, corporation, etc.)
9. Advertising and displaying
10. Management and maintenance wages and salaries
11. Wrapping expenses
12. Light, heat, refrigeration, power
13. Miscellaneous.

The total of these expenses, and any others that an individual store may have, are then apportioned for payment by the customers of each department. The scientific way (which is hardly worth the trouble in a drug store) is to assign rent, heat, refrigeration and possibly others, upon a basis of floor space. Thus, if the prescription department occupies half of the total floor space of the store, its patrons must contribute half the expense for heat, rent, refrigeration, etc. On the other hand, fire insurance is assigned upon the basis of the value of stock in each department, wages and salaries upon the basis of time spent by the worker in each department, etc. The quickest and perhaps the best way of apportioning general overhead is to divide it according to sales. For this purpose the following proportion is useful:

Total Store Sales : Total Rx Dept. Sales :: Total General Overhead : X

X is, then, the share that the prescription department must bear. Since every patron of the department must bear his share of the general overhead, the overhead is divided by the average number of prescription department customers per year. The result is an amount that each customer should contribute. This figure is to be combined with another overhead figure, to be considered next.

The *Prescription Department Overhead* consists of charges similar to and including the following:

1. Narcotic stamp tax
2. Salaries of prescription compounders
3. Taxes upon prescription room property, sales, etc.
4. Druggists' liability insurance premiums
5. Recording, filing, reporting and compulsory prescription copy expenses
6. Depreciation of prescription department equipment
7. Losses through U. S. P. and N. F. changes
8. Losses through incompatibilities, age
9. Amortization of the owner's training, examination and registration costs
10. Library and professional progress expenses
11. Miscellaneous.

The total of these expenses is then divided by the average annual number of prescription patrons. The result is the amount added to the prescription price. Combine both overhead figures into a single one.

Sometimes pharmacists may feel that it is unjust to charge the same amount of overhead to the different types of patrons he serves. In that case he may establish two or three levels for the overhead charge. The drawback here is that he will probably find himself using the low charge too often to allow his customers to pay the overhead.

IV. The Labor Charge.—Filling even the simplest prescription calls for some skill and labor. Make a charge for each of the following:

1. Interpreting the prescription
2. Checking the accuracy of the doctor
3. Compounding the prescription
4. Labeling the prescription
5. Checking the accuracy of the compounding
6. Cleaning the utensils used.

Since one prescription may call for mere counting while another may require complicated manipulation, a uniform charge for labor is not justified. The skill required and exercised is always of the highest degree, so a varying labor charge must be based upon time spent in active compounding. For the present, the labor charge can be figured by multiplying the time consumed in actual work by a rate of $1.80 or $2.00 (or any other rate) per hour.

It is hoped that in the near future enough information can be collected so that a chart of labor charges can be compiled. This chart will allow the pharmacist to find a fair labor charge for his work by merely following a column for the *type* of prescription to a cross column for the *amount* involved. The finished chart can have the following form:

Rate per hour $———

	1 Ounce 6 Units or Less.	2 Ounces 12 Units.	3 Ounces 18 Units.	Etc.
Ready-made				
Liquids				
Ointments				
Folded powders				
Bench-made capsules				
Bench-made suppositories				
Konseals				
Tablet triturates				
Ampuls				
Etc.				

V. The Insurer's Charge.—Unlike many other vendors, the druggist subjects himself to a multitude of legal risks and duties every time he fills a prescription. These legal risks and duties are of two types—criminal and civil—in nature. The criminal, or police power requirements, impose such duties as:

1. Labeling narcotic prescriptions in a particular way,
2. Filing narcotic prescriptions in separate files for stated periods of time,

3. Reporting to federal officers all transactions for the last three months concerning any narcotic or narcotics,

4. Furnishing the doctor or the customer with a copy of the prescription (non-narcotic) upon request,

and innumerable other duties. Breach of any of these duties may mean fines, loss of the right to practice, loss of reputation, loss of business or even a jail term. And the offense need not have been committed maliciously.

On the civil side, the pharmacist is compelled by law in at least one state to be an insurer against injury by his prescription.

In a Kentucky case the court said, "the defendants, being owners of a drug store, *are legally responsible* in damages to the plaintiff *for the accident*, if it was one, and for the outrage, if it was designed." (56 Am. Dec. 568.) Every other state that has had occasion to determine the degree of care a druggist must exercise, has placed that care at an unbelievably high level. As examples: Michigan demands that "the care required be proportioned to the danger involved" (47 Mich. 576); New York insists upon care "in proportion to the gravity of the injury that might result from want of care" (43 Hun 265), and it can be added that injury to the sick is generally greater that that which might result to the well from the same error; Connecticut wants "the highest practical degree of prudence" (85 Conn. 231); and Virginia wants that "degree of care commensurate with danger" (144 Va. 106). As though that were not enough, the common law (like the statutes in some states) requires that the druggist impliedly warrant with every prescription he fills: (1) that the prescription was filled as written (that is, ingredients are accurate as to identity and amount), (2) that the compounder was a registered pharmacist or had equal skill and (3) that the highest degree of care was used in compounding the prescription. All these risks and duties have been shifted from the consumer of the medicine to the compounder; therefore, a pharmacist is entitled to a "premium" for the risks assumed, as is any insurer or risk bearer. This charge is for the risk the pharmacist bears in excess of that covered by druggist liability insurance. In too many cases the jurys' verdict has been far in excess of insurance coverage.

Since the risk the pharmacist bears is determined by the nature and the number of doses or applications in the prescription, the amount of this charge should be based upon these factors. The present system requires such a charge, but as yet has not provided a chart (which is in the process of formation). This chart when completed will have a general form somewhat as follows:

INSURER'S CHARGES.

	6 Doses or Less.	12 Doses.	18 Doses.	Etc.
Ordinary ℞				
Narcotic ℞				
Poison ℞ (Internal)				
Eye ℞				
Sterilized ℞				
Specific				
Etc.				

Until this chart is completed, the druggist should add as an insurer's charge, an amount sufficiently large to raise the final price to a point where material cost does not exceed 25% of it. In other words, the profit, overhead, labor and insurer's charges should be about 75% of the total prescription price. There should also be a set minimum insurer's charge.

VI. The Psychic Charge.—On rare occasions, a druggist must act as a psy-

chologist and help the doctor in convincing the patient that the medicine prescribed is beneficial to him, though it may contain but a small amount of bromide or aspirin, or even no active ingredients. At such times the demeanor of the druggist, and a sufficiently high price will create a confidence in both doctor and pharmacist which cannot be otherwise obtained. The doctor wants and expects this confidence. The amount to add as a psychic charge depends entirely upon the particular case and the judgment of the druggist.

To complete this pricing system a few supplementary rules are necessary or advisable. They follow.

1. When two or more prescriptions are dispensed to the same person at the same time, they should be differently priced.
2. Prescription prices should end in five or zero.
3. Charity and other discounts upon prescriptions should be fixed.
4. Ready-made prescriptions should be priced by the same method used in pricing all other prescriptions.

If the druggist has any doubts about the wisdom of the last rule, let him ask himself the following questions before he fills a ready-made prescription at retail price or retail price plus fifteen cents:

Am I giving him the materials below cost? (material-cost charge)
Am I forgoing my profit? (profit charge)
Am I omitting the overhead charge? (overhead charge)
Am I working for nothing? (labor charge)
Am I assuming the legal risks and duties for nothing? (insurer's charge) (Remember, *you* are liable for any errors caused by a ready-made preparation. The law recognizes *only you*, the druggist, as the maker of the prescription. Has it *your* label upon it?)

In conclusion, the system outlined seems to possess the following advantages:

1. It provides a uniform pricing procedure for all prescriptions.
2. It includes in the price all expenses without duplication.
3. It explains each charge with reference to legal or economic principles.
4. It is subject to revision to meet changing economic conditions.
5. An approximation of one or more of the charges does not affect the accuracy of the other charges.
6. It prevents price variations due to personal variations of clerks.

AN ADVENTURE IN PHARMACEUTICAL CURRICULUM CONSTRUCTION.*

BY HOWARD C. NEWTON.[1]

If you should have an opportunity to construct a pharmaceutical curriculum just as you want it, one which would represent your very best thought on the subject, how would you go about it?

Deans and others have had such an opportunity during the past five years and the results have been interesting and diversified. Doubtless it will be a long time before the full effect of their work is known because we are still feeling the effects of

* Section on Education and Legislation, A. PH. A., Dallas meeting, 1936.

[1] Dean, Massachusetts College of Pharmacy.

the early curricula of the colleges and even of the apprenticeship curricula, if these can be given that title.

It is a real responsibility to prepare a curriculum which may influence greatly the lives of hundreds of young men and women or perhaps an entire profession. Yet the usual method of constructing curricula has been aptly described by Robert L. Kelly, Executive Secretary of the Association of American Colleges, as follows:

> "It is unnecessary to attempt to account for the confusion which has arisen through the former method of curriculum-building, a method, as our investigation shows, which is still the dominant one. A careful scrutiny of the program of study of most of the colleges indicates that they were constructed very much as a tariff bill is constructed in the Congress of the United States. The final result is the outcome of strains and tensions, of concessions and exchanges as between departmental representatives. The evidences that unifying principles are actually functioning in the development of the college curriculum are difficult to discover" (1).

When it became evident some seven or eight years ago that within a few years the curricula of colleges of pharmacy would need to be reconstructed to conform to the four-year plan then proposed, the writer determined to proceed in a manner different from the usual, as described, and to make an extensive study of the preparation of a curriculum for the Creighton University College of Pharmacy. More than three years were devoted to this study and now that all four years of the resulting curriculum have been in effect, it seems that it might be interesting to outline the procedure adopted and the resulting product, the curriculum.

There seemed to be no reason to believe that pharmaceutical education is based on principles different from those of other types of education and therefore it could be expected that the principles formulated by curriculum experts in the general field of education should prove a valuable aid in solving the problem of this study. With this in mind, the writer enlisted the assistance of Dr. William A. Kelly, Head of the Department of Education, Creighton University, who became greatly interested in the project. During the following two years, under his supervision, many formal courses in general curriculum construction and allied educational subjects as well as seminars in the field of education were completed by the writer to furnish a modern background for the work to be done. The following plan of procedure was then adopted:

1. A DETAILED REVIEW OF THE HISTORY OF PHARMACEUTICAL CURRICULUM CONSTRUCTION IN THE UNITED STATES.

This step was taken under the logical assumption that in order to profit by any mistakes which may have been made in the past and to improve upon the current curricula it is necessary to understand how these curricula were evolved. Furthermore, considered in connection with the knowledge of the present, it serves to indicate the trend of progress in this field and to assist in estimating the direction of future developments.

2. THE INVESTIGATION OF THE WORKS OF MODERN EXPERTS IN CURRICULUM-MAKING IN ORDER TO DISCOVER THE GENERAL PRINCIPLES WHICH MAY HAVE BEEN DEVELOPED IN THIS PHASE OF EDUCATION.

In support of this step, the following statement by the Committee on Curriculum-Making of the Society for the Study of Education is quoted:

> "It is the judgment of the Committee that the principles laid down in this general statement on curriculum-making apply equally well to all periods of the American school system. Specifically, we believe the principles are equally applicable, with appropriate adaptations, to the construction of the curriculum of the elementary, the secondary and the college levels. It is only as those who are responsible for the construction of the college curricula come to employ such principles as are herein set forth that we shall have a truly continuous scheme of education" (2).

These first two steps constitute a preliminary survey of the field.

3. A REVIEW OF THE WORK OF CHARTERS, LEMON AND MONELL (3) IN APPLYING THE METHOD OF ACTIVITY ANALYSIS TO THE FIELD OF THE PHARMACEUTICAL CURRICULUM.

This work was done under the personal supervision of W. W. Charters and had for its purpose the securing of completely logical derivation of the content of the curriculum from the determined functions of the materials. The results of such an authoritative and recent investigation appear to form an excellent basis on which to build a pharmaceutical curriculum and they were used for this purpose in this study. The status of such investigations in curriculum planning is termed indispensable by Franklin Bobbitt (4).

4. A QUESTIONNAIRE SENT TO SOME THREE HUNDRED GRADUATES OF THE COLLEGE FOR THE PURPOSE OF OBTAINING DEFINITE INFORMATION AS TO THE PRESENT POSITIONS HELD BY THESE GRADUATES AND ALSO TO SECURE THEIR OPINIONS ON CERTAIN FEATURES OF THE CURRICULUM.

By learning the present occupations of the graduates, it was expected to ascertain the number who were practicing the phases of pharmacy included in Charters' activity analysis or, in other words, to discover whether this activity analysis fits the field occupied by the graduates of this college for which this curriculum was to be made. Furthermore, if any considerable group were found practicing other phases, the curriculum could be prepared to include training for such positions. These graduates whose opinions were sought may be considered to be experts in their own limited field and their opinions should have some weight in constructing a curriculum intended to train students for their positions or similar ones.

5. A SURVEY OF THE CATALOGS OF THE COLLEGES OF PHARMACY OF THE UNITED STATES IN ORDER TO DISCOVER THE SCOPE OF THEIR CURRICULA.

The curricula of these colleges presumably represents the best thought on the subject in the respective colleges and therefore should not be ignored.

6. A REVIEW OF THE REPORTS OF THE NATIONAL DRUG STORE SURVEY.

It was expected that this would yield information of value in outlining the commercial courses of the curriculum.

7. A STUDY OF CHARACTER EDUCATION FROM THE POINT OF VIEW OF THE CURRICULUM.

The importance of character development in education should insure it a place in all considerations such as this. Perhaps it may be considered the outstanding problem in the making of general curricula.

8. THE CONSTRUCTING OF THE CURRICULUM TO CONFORM WITH THE ARBITRARY LIMITATIONS PLACED UPON IT.

Perhaps the most interesting of these steps and the only one which seems to require further explanation for the purpose of this paper is No. 4, the questionnaire. The value of such a questionnaire is recognized by Frederick J. Kelly in his report on a limited survey of the American Arts Colleges (5). This questionnaire, in addition to asking for identification of the graduate as to his present position, asked the following two questions:

1. If you were to attend the College of Pharmacy over again, what subjects would you want in the curriculum, in addition to those which you studied?
2. What subjects did you study which you think should not be included in the curriculum?

It was sent to 302 graduates and the first 250 replies received were tabulated. It is not the purpose of this paper to present the numerous tabulations and charts obtained from the study of this and other steps in the procedure. However, it is of interest to note that in the opinion of these graduates English and Public Speaking courses were very desirable among the non-vocational subjects and that the medical subjects, Biochemistry, Pharmacology and Public Health, deserved additional consideration. Salesmanship and Advertising were favored among the commercial subjects. The one subject which generally did not seem desirable to them was Pharmacognosy.

Turning now to the actual construction of the curriculum from the information available, the following set of objectives was formulated to govern the work:

1. To furnish the student with that basic training which will enable him to render intelligent and constructive pharmaceutical service in the community in which he practices his profession.
2. To prepare the student so that he can grow in information and skill after he graduates and thereby meet satisfactorily the changing demands that occur throughout his service.
3. To offer the student an opportunity to elect certain courses in addition to the prescribed fundamental courses of the curriculum in order that he may better prepare himself for the particular phase of the practice of pharmacy which he may wish to pursue.
4. To develop within the student a professional morale.
5. To exemplify the utilization of the modern methods of curriculum construction and of sound principles of education, general as well as professional.
6. To provide, if possible, for the character education and cultural development of the student.

The arbitrary limitations placed on the work by the by-laws of the American Association of Colleges of Pharmacy and by the University were as follows:

1. The curriculum shall include a period of instruction of four college years.
2. It shall require the completion of not less than 3000 hours (now 3200 hours) of instruction of which at least 1000 hours (now 1300 hours) shall consist of lectures and recitations and at least 1500 hours (now 1300 hours) shall consist of laboratory work.
3. It presupposes the satisfactory completion of four years of high school work or its equivalent.
4. The degree given upon completion of the curriculum shall be Bachelor of Science in Pharmacy, and it is understood that the degree shall be for work which will admit to full standing in the graduate school of any recognized university.
5. It shall include courses in Philosophy.

With these objectives and limitations, this curriculum was constructed as outlined here. The names of the courses indicate their general content in most cases and brief descriptive terms have been included where it seemed necessary. Of course it is not feasible to try to include a complete syllabus with this paper.

In order to show the general plan of the courses, the following diagrams of the major divisions were prepared. These have been found very useful in explaining the divisions of the curriculum to pharmacists and to prospective students and their parents.

CURRICULUM.

Bachelor of Science in Pharmacy.

First Year.

First Semester.	Sem. Hrs.	Second Semester.	Sem. Hrs.
Chemistry 1A (Gen. Inorg.)	4	Chemistry 1B (Gen. Inorg.)	4
Pharmacy 1 (Theoretical)	3	Pharmacy 2 (General)	3
Biology 1 (Botany)	3	Biology 2 (Zoölogy)	3
English 1	3	English 2	3
Pharmacy 8A (Arithmetic)	2	Pharmacy 8B (Arithmetic)	2
Philosophy 1 (Ethics)	2	Pharmacy 7 (Latin)	2
	17		17

Second Year.

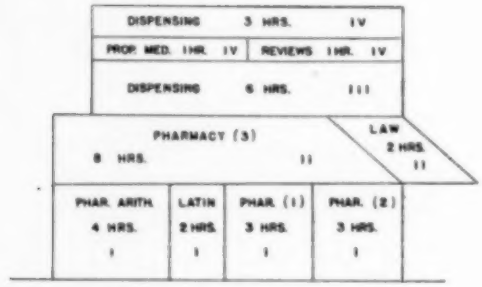
First Semester.	Sem. Hrs.	Second Semester.	Sem. Hrs.
Chemistry 2 (Qual. Analysis)	4	Chemistry 3 (Quant. Analysis)	3
Pharmacy 3A (Manufacturing)	4	Pharmacy 3B (Manufacturing)	4
Biology 3 (Physiology)	3	Pharmacology 1B	2
Pharmacology 1A (Mat. Med.)	2	Pharmacy 9 (Law)	2
Chemistry 4A (Organic)	4	Chemistry 4B (Organic)	4
		Pharmacognosy 1	2
	17		17

Third Year.

First Semester.	Sem. Hrs.	Second Semester.	Sem. Hrs.
Chemistry 5A (Food and Drug)	2	Chemistry 5B (Food and Drug)	2
Pharmacy 4A (Dispensing)	3	Pharmacy 4B (Dispensing)	3
Biology 4A (Bacteriology)	3	Biology 4B (Bacteriology)	3
Pharmacognosy 2	2	Philosophy 2 (Psychology)	2
Pharmacology 2 (Mat. Med.)	2	Pharmacology 3 (Mat. Med.)	3
Approved Electives	4	Approved Electives	4
	16		17

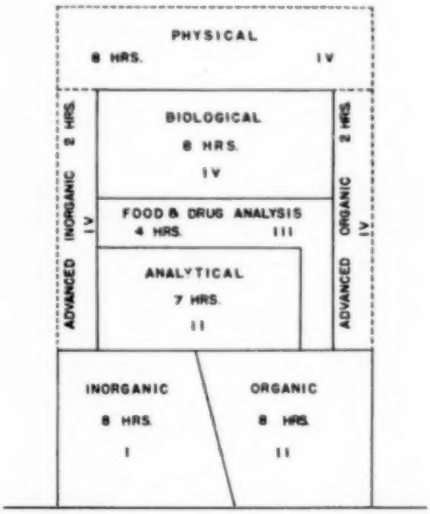
Fourth Year.

First Semester.	Sem. Hrs.	Second Semester.	Sem. Hrs.
Pharmacy 5 (Dispensing)	2	Pharmacy 5 (Dispensing)	1
Chemistry 7A (Biochemistry)	4	Chemistry 7B (Biochemistry)	4
Public Health 1A	2	Public Health 1B	2
Pharmacy 10 (Proprietaries)	1	Pharmacy 12 (Reviews)	1
Philosophy 3 (Applied Ethics)	2	Pharmacology 4	1
Approved Electives	7	Approved Electives	7
	18		16


DISPENSING 3 HRS. IV
PROP. MED. 1 HR. IV
REVIEWS 1 HR. IV
DISPENSING 6 HRS. III
PHARMACY (3) 8 HRS. II
LAW 2 HRS. II
PHAR. ARITH. 4 HRS. I
LATIN 2 HRS. I
PHAR. (1) 3 HRS. I
PHAR. (2) 3 HRS. I

ROMAN NUMERALS INDICATE THE YEAR OF THE CURRICULUM

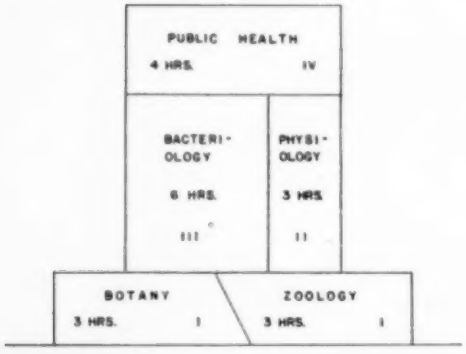
GENERAL PLAN OF THE COURSES IN PHARMACY


PHYSICAL 8 HRS. IV
ADVANCED INORGANIC 2 HRS. IV
BIOLOGICAL 8 HRS. IV
ADVANCED ORGANIC 2 HRS. IV
FOOD & DRUG ANALYSIS 4 HRS. III
ANALYTICAL 7 HRS. II
INORGANIC 8 HRS. I
ORGANIC 8 HRS. II

ROMAN NUMERALS INDICATE THE YEAR OF THE CURRICULUM

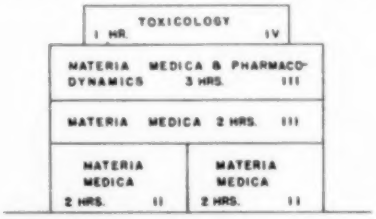
BROKEN OUTLINE INDICATES AN ELECTIVE COURSE

GENERAL PLAN OF THE COURSES IN CHEMISTRY



ROMAN NUMERALS INDICATE THE YEAR OF THE CURRICULUM

GENERAL PLAN OF THE COURSES IN BIOLOGY


TOXICOLOGY 1 HR. IV
MATERIA MEDICA & PHARMACODYNAMICS 3 HRS. III
MATERIA MEDICA 2 HRS. III
MATERIA MEDICA 2 HRS. II
MATERIA MEDICA 2 HRS. II

ROMAN NUMERALS INDICATE THE YEAR OF THE CURRICULUM

GENERAL PLAN OF THE COURSES IN PHARMACOLOGY

Approved Electives.

Third Year.

Modern Language (French, German, Spanish)
Economics 11 and 12 (Principles of Economics)
Mathematics 2 (Trigonometry)
Speech 51 (Public Speaking)

Fourth Year.

Accounting 1 (Elementary Accounting)
Advertising and Selling 1 (Advertising)
Advertising and Selling 2 (Show Card Writing)
Advertising and Selling 3 (Window Display)
Advertising and Selling 4 (Salesmanship)
Physics 21 and 22
Pharmacognosy 3 (Advanced Pharmacognosy)
Pharmacy 6 (Commercial Pharmacy)
Pharmacy 11 (Druggists' Sundries)
Pharmacy 13 (Cosmetics)
Pharmacy 14 (Veterinary Remedies)
Public Speaking 51 and 52
Chemistry 6 (Advanced Organic).

Other courses given in the colleges of the University may be accepted as approved electives at the discretion of the Faculty of the College of Pharmacy.

This curriculum was not offered as something fixed and unchanging in the years to come; on the contrary, it was expected that refinements and adjustments would be made through continuous study, evaluation and testing of materials of the curriculum and that it would keep pace with the progress and practice of the craft.

It will be noticed that the first two years of the curriculum are made up entirely of required courses; the third year includes eight hours of electives and the fourth year, fourteen hours of electives. It is considered to be a fact that the courses of these first two years are necessary as a foundation for the practice of pharmacy in each of its phases. Therefore the administration of the first two years is practically automatic.

At the end of the second year it is planned that the student shall attempt to decide which phase of the practice of pharmacy he wishes to pursue after graduation. By means of conferences with the student, all available information on each phase will be brought to his attention and all possible assistance will be given him in order to attempt to insure a wise choice. It is expected that the student will have made his decision before the date of registration of his third year. Upon this decision will depend the choice of elective courses which he will be advised to select. Thus, if he decides on the commercial practice of pharmacy, his electives will include the courses of the commercial group; if he wishes to prepare to enter the field of pharmaceutical chemistry, the electives in Chemistry will be advised; if he plans to enter a school of Medicine, his electives will be taken from the group commonly known as pre-medical subjects, such as Physics, Modern Foreign Language, etc. The electives of the fourth year follow out the plan indicated for the third year or in case of a change of mind on the part of the student, will lead in the direction which seems best adapted to his individual needs.

For the proper administration of this curriculum it is deemed necessary that the administrator continue to gather all available information on the phases of the practice of pharmacy so that the advice which he may give the student will be accurate at the time given. This may cause changes in the approved electives from time to time in order to meet the conditions in the several divisions of the practice.

Four years have now passed since this curriculum became effective and we can consider as completed the most important part of our adventure.

The writer, in presenting this paper, hopes to encourage discussion of the subject and perhaps to stimulate others to describe their experiences in constructing a curriculum for use during the past four years. It is not presented with any thought of attempting to regiment college curricula but with the thought that some point mentioned might lead to an improvement of them. As an example, even if it were not to be acted on immediately in making changes, wouldn't it be interesting to have the opinions of our graduates from time to time as expressed in answer to a questionnaire like the one described here? We might gain the assurance that we are offering just what is best for our students and then again we might be given reason to doubt it. In any event, it would help in eliminating the obsolete portions of a curriculum and in curtailing a division of it which may have come to receive too great an emphasis.

In conclusion, believing that progress in the development of the pharmaceutical curriculum is a good criterion of the progress of the profession, we suggest that an increased interest in the subject on the part of those in each and every phase of the profession, instead of just the few in the field of education, will result in still greater future progress.

REFERENCES.

(1) *Bulletin*, Association of American Colleges, page 71 (April 1923).
(2) The Twenty-Sixth Yearbook National Society for the Study of Education, Part II, page 12.
(3) Charters, W. W., Lemon, A. B., and Monell, Leon M., "Basic Material for a Pharmaceutical Curriculum."
(4) Bobbitt, Franklin, "How to Make a Curriculum," page 5.
(5) Kelly, Frederick J., "The American Arts Colleges," page 198.

PROGRAM OF NATIONAL CONFERENCE ON PHARMACEUTICAL RESEARCH, 1937 MEETING, NEW YORK, N. Y., AUGUST 14TH AT HOTEL PENNSYLVANIA.

FIRST SESSION, 2:00 P.M.

1. Call to Order by the Chairman.
2. Appointment of Nominating Committee.
3. Summary of Year's Activities and Outlook of Conference for the Future, by Chairman Gathercoal.
4. Reports of Officers. *a*. Report of Secretary. *b*. Report of Treasurer. *c*. Report of Executive Committee by Secretary.
5. Reports of Standing Committees.
   (1) Physical Chemistry, Arthur Osol, *Chairman*.
   (2) Bacteriology and Immunology, Louis Gershenfeld, *Chairman*.
   (3) Pharmacognosy, Heber W. Youngken, *Chairman*.
   (4) Pharmacology and Bioassays, James C. Munch, *Chairman*.
   (5) Medicinal Chemicals, Joseph Rosin, *Chairman*.
   (6) Endocrinology, Arthur Grollman, *Chairman*.
   (7) Manufacturing Pharmacy, L. Wait Rising, *Chairman*.
   (8) Pharmaceutical Dispensing, William J. Husa, *Chairman*.
   (9) Educational Methods, A. B. Lemon, *Chairman*.
   (10) Pharmaceutical Economics, Harry S. Noel, *Chairman*.
   (11) Historical Pharmacy, Charles H. LaWall, *Chairman*.
   (12) Census of Research, James C. Munch, *Chairman*.
6. Reports of Other Special Committees. 7. Roll Call of Delegates.
8. Adjournment for Dinner. Arrangements Will Be Made for a Dinner for the Delegates Assembled.
   An address pertinent to the work of the Conference will be delivered.

EVENING SESSION, 8:00 P.M.

9. Symposium on Deterioration.
   a. Digitalis Preparations, James C. Munch.
   b. Pepsin Preparations, E. N. Gathercoal.
   c. Ergot Preparations, M. J. Thompson.
   d. Syrup of Ferrous Iodide, William J. Husa.
10. General Discussion of the Status of Pharmaceutical Research.
11. Election and Installation of Officers. 12. Adjournment.

Chairman, E. N. GATHERCOAL; *Secretary*, JOHN C. KRANTZ, JR.

THE DEPARTMENT OF THE AMERICAN ASSOCIATION OF COLLEGES OF PHARMACY

The Publication Board

RUFUS A. LYMAN, *Chairman and Editor.* ZADA M. COOPER, *Secretary.*
ERNEST LITTLE, ANDREW G. DUMEZ, CHARLES B. JORDAN, ROBERT C. WILSON.

(Two timely subjects are discussed in the Departmental pages this month. The question of women in pharmacy was made so by the last annual report of the Chairman of the Executive Committee of the American Association of Colleges of Pharmacy. As a result of that report the Association was stampeded into the appointment of a committee to find out if women really do present a problem in pharmacy. A report will be made at the New York meeting.

The question of hospital pharmacy has been a growing one for years. Just now its importance is increased by the establishment of hundreds of smaller hospitals throughout the country and the general recognition of the fact that a hospital, whatever its size, is not a complete hospital without a pharmaceutical service. Furthermore, the fact that a section on hospital pharmacy has been established by the AMERICAN PHARMACEUTICAL ASSOCIATION is indicative of the growing importance of this phase of pharmacy's professional service. These facts justify the publication of the papers by Dr. Nellie Wakeman, Mr. Louis Z. Zopf and Dr. L. D. Edwards, previous to the annual meetings of the Associations which are interested.—*The Editor.*)

WOMEN IN PHARMACY.

BY NELLIE A. WAKEMAN.*

Having been for quite some time a woman engaged in a pharmaceutical occupation, I have, naturally, long been interested both in women pharmacists and in the opportunities offered to them in the various lines of pharmaceutical activity. It is doubtless for this reason that Dean Lyman asked me, a few days ago, to write something on this subject for the *American Journal of Pharmaceutical Education.*

I did not attend the meeting at Dallas last summer, and until Secretary Cooper relayed President Crockett's request that I serve upon the new special committee on the Status of Women in Pharmacy, I had always looked upon the problems of women in pharmacy as those of the women themselves and not of the profession in general. It appears now that the number of women students entering colleges of pharamacy is increasing; in the year 1935 out of a total of 2347 new students entering the colleges a little over ten per cent were women, and the matter now becomes a problem of major importance, calling for the creation of a special committee to study it. I say of major importance because, in the report of the Executive Committee, as printed in the *American Journal of Pharmaceutical Education,* out of eleven pages discussing the problems affecting pharmacy as a whole, two pages, lacking a few lines, are given over to the question of women in the profession.

I accepted an appointment to this committee with alacrity, because I was convinced that from my long experience as a woman in pharmacy and from my intimate contact with women pharmacists, both in and out of college, I should have something of value to add to the discussion.

In my work with students of pharmacy I have not looked upon them as either men or women, but as students, and I have tried to judge them according to how well

* Course in Pharmacy, University of Wisconsin.

they accomplish whatever they are expected to do. If they make good, that is what we expect of them; but if for any reason they fail, being women does not excuse them, and being men does not justify their failures. In college work men and women are nearly on a par so far as opportunities go, but even as college students men have the best of it. They have the advantage of physical strength, to say nothing of the traditions and practices of our man-made institutions, ordained by men for men. Notwithstanding their disadvantages women are able to hold their own with men as students of pharmacy.

On my desk before me there is a copy of a report for the second semester of 1935–1936 compiled by the office of the Dean of Men of the University of Wisconsin, from which a few statistics are taken; I am not unaware of the fact that statistics may be made to prove almost anything. These figures, however, coming as they do from a source prejudiced in favor neither of women nor of pharmacy students, may be of value in comparing the standing of women pharmacy students with men in the same courses, and also with other students in the University.

During the semester under consideration there were enrolled in the University of Wisconsin 7266 undergraduate students. They attained a grade point average of 1.546. Of these 95 were pharmacy students with a point average of 1.584. Of the 95 pharmacy students 74 were men and 21 women, considerably more than the 10 per cent included in the United States at large. The 74 men students in pharmacy earned a point average of 1.568 and the 21 women students of 1.645. So much for the ability, and the success of women as pharmacy students at one of the colleges of pharmacy.

After leaving college, women are at a greater disadvantage than as students. In the first place it is more difficult for them to get jobs, but that is not a problem peculiar to pharmacy. In every occupation in which women come into competition with men the same condition prevails, and in many professions it is worse than in pharmacy. This is a problem which women everywhere have to meet; they expect it and their expectations are fully realized. Women are slowly solving this problem for themselves, grateful, however, for whatever help or encouragement they receive from others, and they will, increasingly, continue to do so if no greater obstacles are placed in their way. The best advice that can be given to women in pharmacy, or in any other occupation which men find desirable, is to prepare themselves as completely as possible for the work they are to perform. Whenever a woman comes into competition with a man she must not only be as good but considerably better than the man who wants the same job. Even then the chances are about ten to one that it will be given to the man, and if the woman does get it, her salary will probably be less than that paid to men for the same work; moreover, arrangements are sometimes made that whatever of honor or credit accrues to the position will be directed to some male superior or colleague.

Now let us consider briefly the nature of the difficulties in the way of women seeking desirable positions. *First*, there is the age-old superstition of woman's inferiority to man in all occupations except those indicated by the Kaiser's three K's, "Kirche, Kueche und Kinder." Deny it as they may, most men and not a few women are still bound by this superstition. Next, there is a solidarity among men, a sort of a loyalty of man to man, which resents woman's intrusion into fields so long held by man alone. As competition increases, so does this feeling increase, and

it is this which so frequently results in the employment of a man, clearly inferior in every respect, in preference to a better qualified woman. Finally, there are the limitations as to hours of employment, placed, both by law and by custom, upon women, indiscriminately, in work outside the home. These restrictions, imposed by a well-meaning but sometimes thoughtless public, intended for the protection of women, frequently work a real hardship upon them.

After the woman pharmacist has been educated and has secured her job does she make a good pharmacist; does she serve the public acceptably and adequately, and is she, herself, injured by the work? Here I may be permitted to quote from the Report of the Chairman of the executive Committee:

> "I believe we all agree that pharmacy is a profession in which women can very well take the place of men, except perhaps in the heavier work connected with a commercial store. However, in most stores this heavier work is done by a janitor, so that this objection is not valid."

Now that we have a special committee to continue the work begun by Dean Jordan, what shall this committee do? That, of course, is for the chairman to decide. A few suggestions as to lines this investigation may well follow have been made to me by others interested in the matter, though not members of the committee. Among these suggestions are the following: The study as to numbers of women in pharmacy should, if possible, cover more than five years, and ten would be better, in order that it may include more than the so-called depression years. It should go, not only into the number of women entering colleges, but even more carefully into those graduating, and also those graduates who actually enter pharmaceutical occupations, and how long they remain in this work. The number of graduates who go into positions already waiting for them may also well be taken into account. Daughters of pharmacists who enter their fathers' stores, and Sisters of Charity who become pharmacists in the hospitals of their orders, surely create few problems for the profession as a whole. These are some of the considerations which may substantially reduce the ten per cent of women pharmacists with which the profession is now faced.

After all these things have been taken into account, should there prove to be a full ten per cent, or even a greater number of women in pharmaceutical pursuits, is this necessarily a calamity so long as they are good citizens and good pharmacists? Some one, it is stated in the report of the Chairman of the Executive Committee, has objected to the employment of women on the grounds that he cannot use them to close up his drug stores after eleven o'clock at night. If there were twenty per cent, or even fifty per cent of women pharmacists, there would yet be men left to do this, should that undesirable necessity still exist. As a matter of fact, isn't the keeping open at all hours of night a greater evil than the presence of women in the profession?

The entrance of women into pharmacy, as, indeed, into all occupations, is but a part of a great world movement for the intellectual, political and economic emancipation of women. We are now in the third, and in some respects the most difficult, phase of this movement, one in which each woman has to work out her own individual salvation. This part of the movement, like the others, will go on. Difficulties placed in its way retard, but they will neither discourage nor stop it. Just as women have won for themselves a fair measure of educational and political

equality, they are now struggling to gain economic equality—the right of every woman to earn her own living in her own way. And when this right has been once attained, have no fear, for it will not be abused any more than have been those other rights so dearly won.

DISCUSSION.

In discussing the question of women in pharmacy, Dean C. W. Johnson of the University of Washington, says: "Women have had to fight for everything that the sex has gained in the nature of equality with men, in political, social and professional life. They have been in pharmacy for many years with about the same range of success as men, hence at the present time they present no new problem. For many years the University of Washington College of Pharmacy has had from ten to twenty per cent women students, hence the problem (?) of women in pharmacy is not new in this state."

There has been little difficulty in placing women graduates in work they are prepared to do. A considerable number of druggists in the State of Washington ask for women graduates when help is needed. Some of the leading prescription stores of the state use women pharmacists largely, and in so far as is known the pay ranks well with that given men of the same experience. Hospitals almost invariably use women in the pharmacy. Some women go on with graduate work or complete the required courses in education and find employment as science teachers in high schools.

The same conditions apply in finding employment for women as for men. The question of personality is of prime importance. Is the individual woman (or man) of attractive appearance, does she dress neatly and modestly, and has she the ability to lead people to have confidence in her work? If the graduate has these traits fairly well developed and if the faculty of the college can say that she is honest, accurate, industrious and willing to serve both the public and her employer, there is no question of employment within a reasonable time after graduation. In general, women rank well with men in intelligence and in ability to complete a rather difficult course requiring long hours in the laboratory and careful preparation of class room work.

There is another point, however, regarding pharmaceutical education that should be mentioned. Let us assume first, that the high school graduate, man or woman, is interested in science. If this interest centers either in the physical or biological sciences, what course touching these subjects is better for the student than a well-organized pharmacy curriculum? Will any pharmacy teacher admit that he cannot conduct his classes so as to impart cultural as well as professional instruction? Must a subject be strictly non-informational to have culture value? Certainly science teachers will insist that their subjects do have both informational and cultural value. The subject of pharmacognosy, for example, will lead the student to a broader viewpoint of nature. The student in this subject will learn something of geography, commerce, mythology, history, of plants as sources of interesting constituents, and when this knowledge is properly organized he has gained some culture as well as necessary and useful information. Other subjects in the pharmacy curriculum can be made just as interesting as well as of practical value in earning a living.

Granting that a graduate in pharmacy does acquire culture as well as practical information, why not assume the same attitude as teachers in liberal arts colleges in regard to employment? The liberal arts college does not worry about placing graduates. It tries to train and develop the mind of the individual and thinks little of some special position. The college of pharmacy, therefore, not only opens the possibility of definite employment but also does everything else for the student that any other type of curriculum can do. Let me repeat that the student should be interested in science, and if so, why worry about employment.

Women, in general, think of marriage as their ultimate career. If again the woman is interested in science, will any other science course better fit her for the home than training in pharmacy? The fact remains that a woman graduate in pharmacy is as well prepared for her life career, be it what it may, as any other type of science graduate. The faculty of a pharmacy college will usually try to find employment for all of its graduates but it should not worry about employment or discourage women from entering as students. The main thing is to give fundamental instruction that will develop the student and leave the question of employment in the background.

Professor Ina Griffith, of the University of Oklahoma, comments as follows:

"In Oklahoma our women graduates have not presented a special problem. The women graduates of the school of pharmacy average about ten per cent of the graduating classes. They have found places in practically every branch of the profession. They go into retail business as successful proprietors of stores and as pharmacists. They are in hospital pharmacies, both in the drug dispensing and technician departments. We include in our curriculum training for technicians and our women are interested in it and capable. Our women graduates are also filling positions in technical drug laboratories and in the teaching profession. In Oklahoma the supply of women has never caught up with the demand."

HOSPITAL PHARMACY.

BY LOUIS C. ZOPF.*

For many years hospital pharmacists have been active in the Section on Practical Pharmacy and Dispensing of the AMERICAN PHARMACEUTICAL ASSOCIATION. The establishment of a sub-section provides a specific place for the discussion of problems directly related to this branch of pharmacy.

Increasing demands are being made of the Hospital Pharmacist. His basic training must be of the best. His knowledge of newer products and research progress must be up-to-date. This increasing demand may be a natural evolutionary process, but the stand taken by the American Colleges of Surgeons in their minimum standards for a Hospital Pharmacy and the editorial in "Hospitals," *Journal of the American Hospital Association*, have helped much. As early as October 1932, a resolution by the Council on Medical Education and Hospitals of the American Medical Association evidenced a need for adequate supervision of Hospital Pharmacies. The resolution as adopted was,

* State University of Iowa.

"*Resolved:* That a change be inserted in the 'Essentials of a Registered Hospital' requiring that the pharmacy of a hospital should be adequately supervised and should comply with state laws."

Who is concerned in this problem of the hospital pharmacist? The answer, I believe, is —*firstly*, the hospital pharmacist himself, *secondly*, the teachers in our colleges of pharmacy and *thirdly*, the other members of the pharmaceutical profession.

The hospital pharmacist must use a bit of introspection and without prejudice analyze, *firstly*, his adaptability for this type of work; *secondly*, his qualifications for the tasks he is required to perform; *thirdly*, his ability to work with medical men and that without an inferiority complex; and *fourthly*, the completeness of the service he extends to the hospital. There are other important factors, but these appear as paramount. They must and can be answered by the hospital pharmacist.

The colleges of pharmacy have a vital part in the development of better hospital pharmacists and pharmacies. Whenever possible, colleges should have a connection with a hospital where their students can obtain some experience in hospital dispensing. This pharmacy should be under the supervision of a registered graduate pharmacist who is approved by or is a member of the staff.

Sufficient training in hospital pharmacy should be made available to all students so they may determine whether they desire this branch of pharmacy as their life's work. Such training is essential and fundamental. All students of pharmacy, regardless of their future intentions, can profit by such a course.

Duties of the hospital pharmacist vary with the size and type of hospital he serves. Some are required to do bacteriological and pathological work. Others are kept busy with the compounding and dispensing. Some are requested to assist in the instruction of materia medica for nurses and to offer assistance to interns in prescription writing. Detailing the medical staff on U. S. P. and N. F. preparations and assisting in formulary specifications are very important essentials. Many are required to purchase drugs and supplies and, therefore, must understand methods of stock control and storage. These and many other special duties are going to require that graduate courses be offered in such subjects; for, as the demands increase so must the ability and the quality of the pharmacist advance.

The opportunities for hospital pharmacists are increasing. We have more hospitals, people are overcoming the hospital-shy attitude, doctors in the country towns no longer perform their surgery in the home or office, but seek the facilities of a hospital. Opportunities for research and coöperation with other health professions are many. The equipment of the modern hospitals with the constant care of nurse and resident physicians, the diagnostic laboratories and X-ray equipment mean but one thing—graduate registered pharmacists must be on duty to properly prepare and dispense medication for these patients.

The wards and laboratories require routine pharmaceuticals and chemicals. Parenteral solutions must be prepared and sterilized. Hospitals are requiring adequate supervision of their pharmacies. They should have had it long ago. Interns and nurses have a definite place in the hospitals, but not in the pharmacy.

As to other members of the profession, it is evident that through hospital pharmacy we have one of the strongest links with our allied profession, medicine. This test can be strengthened or broken, depending upon the type of people who

represent our profession in this field. The best people are needed, but they must be backed by a profession consisting of men and women representing pharmacy at its best. Every individual is a representative, and it is necessary that they conduct themselves so that no reflection be cast on the profession.

Retail pharmacists are realizing that if their businesses are to survive they must get back to professional pharmacy. This move will strengthen the standing of our profession; it will rebuild confidence in the public and develop a definite need and service for the medical profession.

Much ground work is necessary for the building up of a strong organization. In this direction we have attempted to advise all hospital pharmacists about the establishment of this sub-section, but it is possible that many were not reached, as a complete list of pharmacists so employed was not available.

I wish to thank the deans of the colleges of pharmacy for their coöperation in supplying a list of their graduates who are employed in hospital pharmacy.

Our program at New York will be composed of papers dealing with the every-day problems of hospital pharmacists and, in addition, we hope to have an expression from the Pharmacy Committee of the American Hospital Association as to their needs in pharmaceutical service. Further, it is expected that some interesting information will be supplied in regard to hospitals now entirely without pharmaceutical service. Another important point for consideration is that of working out the details of the minimum standards for a hospital pharmacy. These problems require that all pharmacists become active and take an interest in this work; we have taken a forward step, and through coöperation with the American Colleges of Surgeons, American Hospital Association and American Medical Association we have a great opportunity for the extension of pharmaceutical service.

Dean Edward Spease, Secretary E. F. Kelly, H. A. K. Whitney and others are taking an active part in this work and we are encouraged by the interest of Hospital pharmacists and others.

A GRADUATE COURSE IN HOSPITAL PHARMACY.

BY LEROY D. EDWARDS.*

The recent developments in hospital pharmacy have been extensive and rapid. The American College of Surgeons and the Catholic Hospital Association of the United States and Canada have adopted "Minimum Standards for a Hospital Pharmacy."[1] The American Hospital Association appointed a Committee on Pharmacy during 1936; a like committee will function during 1937. The AMERICAN PHARMACEUTICAL ASSOCIATION has established a sub-section on Hospital Pharmacy. These steps all point to the immediate future developments of pharmacy in the hospital, and definitely offer one interested in professional pharmacy an opportunity for action.

Immediately, a number of questions present themselves. Will the present-day pharmacy school graduate be able to meet the requirements as this movement grows? Will the hospitals of the future ask for better trained pharmacists? If so,

* School of Pharmacy, Western Reserve University.

[1] *Bull. Am. Coll. Surg.*, 21, 202 (Oct. 1936).

what will be the source of these better trained pharmacists? Since there is no place in the field of pharmacy where the need of properly educated and trained men is more essential, it stands without question that the hospitals will demand the highest type of pharmacist available. The answer to the question as to the source of these men is, for the moment, most difficult.

Some have already advocated that the education of the hospital pharmacist should more closely approach that of the physician. Such a hospital pharmacist, especially those in teaching hospitals and in hospitals associated with universities, will be expected to produce pharmacy's share of research. He must be equipped to manufacture pharmaceutical products of all kinds on a scale large enough to satisfy hospital needs. He must be able either to do or to direct the analytical work necessary in standardizing his products both chemically and biologically. In a hospital that does not maintain a bacteriological laboratory he must be prepared to make many tests and checks, and where one is maintained, he must know wherein it is useful to his work. Certainly he will be called upon to prepare the many stains used in biological and diagnostic tests. He must have a knowledge of drugs and supplies that will qualify him to form specifications for buying even if he does not perform the act of buying. He must be familiar with the use and availability of professional supplies, *i. e.*, instruments, rubber goods, gauze, etc., to the end that the nurse and the surgeon have at hand all needed equipment. He must be able to prepare and sterilize parenteral medications. He must be acquainted with all the departments of a hospital and their functions in order that he may know exactly where the pharmacist fits into the whole. With such a background, he will better understand the physician's work and needs—he will truly become a physician's helpmate. And, above all, he can be given the proper recognition which is so necessary for the future progress of hospital pharmacy.

Throughout the present school year the staff of the School of Pharmacy and the pharmacist of the University Hospitals of Western Reserve University have given this problem considerable thought. As a result of this work a list of courses available to those who wish to do graduate work with a major in hospital pharmacy has been submitted for publication in our *Graduate School Bulletin* of June 1937. Such a student may select courses in analytical pharmaceutical chemistry. He may serve in the several departments of the hospital pharmacy which is composed of a large out-patient department filling 65,000 prescriptions annually, a utility drug corridor, the pharmacy proper, the professional stores and the parenteral solution room. He will have the opportunity to receive instruction in bulk hospital manufacturing and control work as carried out by the laboratories located in the School of Pharmacy. In addition many related courses such as biochemistry, bioassays, microscopy, problems in compounding, pharmacology, bacteriology, etc., will be available.

Such a program as outlined above is made possible by the fact that the School of Pharmacy of Western Reserve University is responsible for the conduct of the pharmacy and enjoys the sole privilege of pharmaceutical research in The University Hospitals of Cleveland.

The American Association of Colleges of Pharmacy meets August 16th, in New York City.

PROCEEDINGS OF THE LOCAL BRANCHES

"All papers presented to the Association and Branches shall become the property of the Association with the understanding that they are not to be published in any other publication prior to their publication in those of the Association, except with the consent of the Council." —Part of Chapter VI, Article VI of the By-Laws.

ARTICLE III of Chapter VII reads: "The objects and aims of local branches of this Association shall be the same as set forth in ARTICLE I of the Constitution of this body, *and the acts of local branches shall in no way commit or bind this Association, and can only serve as recommendations to it.* And no local branch shall enact any article of Constitution or By-Law to conflict with the Constitution or By-Laws of this Association."

ARTICLE IV of Chapter VII reads: "Each local branch having not less than 50 dues-paid members of the Association, holding not less than six meetings annually with an attendance of not less than 9 members at each meeting, and the proceedings of which shall have been submitted to the JOURNAL for publication, may elect one representative to the House of Delegates."

Reports of the meeting of the Local Branches shall be mailed to the Editor on the day following the meeting, if possible. Minutes should be typewritten with wide spaces between the lines. Care should be taken to give proper names correctly and manuscript should be signed by the reporter. *Please advise us of changes in Roster and mail reports promptly.*

BALTIMORE.

The April meeting of the Baltimore Branch, AMERICAN PHARMACEUTICAL ASSOCIATION, was held April 8th, at the School of Pharmacy, University of Maryland. Thirty-five members and guests were present.

This meeting was opened by President A. N. Hewing; and after routine matters were disposed of a communication from Dr. Adolph Ziefle, Chairman of the AMERICAN PHARMACEUTICAL ASSOCIATION Committee on Local Branches, was read to assembled members by the Secretary. A résumé of the last annual report of this committee was also presented. Those recommendations of this national committee to the various local branches which had reference to the furtherance of the cause of professional pharmacy through the presentation of professional programs at State pharmaceutical association meetings under AMERICAN PHARMACEUTICAL ASSOCIATION Branch auspices required little discussion. The Maryland State Pharmaceutical Association having included such programs at its annual conventions for a number of years, and members of the Baltimore Branch having been active as individuals in the presentation of these programs, it was decided that no organized effort on the part of the Local Branch would be necessary to carry out the recommendations noted.

Our guest speaker for the evening was Sam Y. Althoff, director of Biological Promotion for the Sharp and Dohme laboratories. The topic announced for discussion by Mr. Althoff: "The Romance of Biological Production" proved to be an apt title for the address which followed. This included a review of historical mile-stones in the discoveries and researches leading up to our present use of and dependence on biological products as a means of combating infectious diseases, and an enlightening description of methods followed in the production of some typical items of this group.

In reviewing the history of the use of vaccines, antitoxins, serums, etc., in the treatment of disease, the speaker referred to conditions existing in the early years of the nineteenth century and cited the appalling death rate recorded during the frequent sweeping plagues of smallpox and other infectious diseases then ravaging European countries. He recalled that the development of a vaccine for combating the dreaded smallpox by Jenner in Germany, in 1798, resulted from the observation of the fact that milkmaids who had contracted the infectious disease cowpox from cattle were usually immune to human smallpox. Serum obtained from pustules on these diseased cattle provided the first vaccine discovered for human use; and marked the beginning of the development of preventative medication.

An outline of the modern method of production for smallpox vaccine was given, with an explanation of necessity for the extreme care, caution and cleanliness used in order to avoid contamination of the vaccine with virulent organisms such as staphylococcic and streptococcic bacteria.

Other mile-stones in the conquest of bacterial diseases noted were the development of a vaccine treatment for rabies by Pasteur, and the production of typhoid vaccine in 1894 by Wright, in England. The latter development marked the beginning of present-day bacterial vaccine therapy. Bacterial vaccines represent the simplest form of biological now in use, but the so-called sensitized bacterial vaccines are later and more complicated products. The history and description of rabies vaccine was given by the speaker in his discussion of these products.

The discovery and isolation of the bacillus of diphtheria opened up a new field in the development of biological products. The production of a diphtheria antitoxin in Germany in 1894 marked a great forward step. The speaker recalled the skepticism and doubt which met the announcement of this development; and difficulties encountered in this country when production of diphtheria antitoxin was first started in Philadelphia. Physicians were skeptical, and no market existed for the first antitoxin produced. It was not until after the antitoxin was used on a desperate case in a Philadelphia hospital, and the patient recovered, that a few physicians could be induced to try this method of treating diphtheria. This early cool reception of antitoxins was contrasted with the present universal acceptance of such products, and the further wide-spread use of later developments such as the diphtheria toxoids and similar preventative treatments.

The final biological products described and discussed were the snake-bite antivennins. One interesting fact brought out regarding these products was in connection with the necessary dosage. A small child may require more antivennin to neutralize the toxins injected into tissues when bitten by a poisonous snake than would normally be required to protect an adult from its effects. This was explained as due to the lessened quantity of blood in the small body as compared with an adult, and the lessened capacity for production of antibodies in the smaller body. It would be well to keep this fact in mind.

At the conclusion of the address, Mr. Althoff answered several questions asked by members present. The speaker was congratulated on his excellent presentation by President A. N. Hewing, who tendered the thanks of the Branch.

The meeting was then adjourned, and a short social session held at which refreshments were served.

R. S. FUQUA, *Secretary.*

NEW YORK.

The last meeting of the Spring season of the New York Branch of the A. PH. A. was called to order at 8:40 P.M. on May 10, 1937, in Columbia University, College of Pharmacy. About one hundred members and guests were present. President F. C. A. Schaefer presided.

The minutes of the April meeting were read and approved. Treasurer Currens reported a balance of $435.38.

Dr. Kidder, Chairman of the Committee on Professional Relations, reported that in furthering the program to increase the use of the U. S. P. and N. F. preparations, copies of the N. Y. S. Pharmaceutical Association pamphlet on official preparations had been sent to all physicians in the Bronx.

Chairman Lehman, of the Committee on Education and Legislation, reported as follows:

"The Miller Tydings Bill, H. R. 1611 has been shelved temporarily by order of President Roosevelt. On April 26th the Chief Executive directed a letter to Congress asking that further consideration of the measure be delayed. This action has caused much dismay among the protagonists of the movement for strengthening the Fair Trade laws of the nation, for inasmuch as forty states have a Fair Trade law on their statute books, the defeat of a Federal Law will prevent the enforcement of the laws materially, as the Federal Law is necessary to enforce the same under Interstate Commerce. The State laws require that the firms issuing minimum resale price contracts must be domiciled in such states, which would be a costly proceeding for small manufacturers, and discourage them from issuing contracts.

"The N. A. R. D. is up in arms against the action of the President and earnestly requests all Associations, as well as influential individuals, to write to the Chief Executive asking him to favor the passage of the bill, in spite of the fact that the Federal Trade Commission is reputed to have threatened suit under the Anti-Trust Laws against such manufacturers who issue contracts under Interstate Commerce. The N. A. R. D. also suggests that the Governor of the State be petitioned to urge the President to favor the Miller Tydings Legislation."

(Chairman Lehman reported from the monthly bulletin of the California Pharmaceutical Association various manufacturers who had accepted Fair Trade.)

"One law was passed at this session which was not sponsored by the State Association, namely, the Narcotic Act amendment which strengthens the existing law materially, provides more inspectors, etc. I have no news as to what the regulations will be under the law, but understand that it will be a duplication of the Harrison Law. I am informed that a board will be created under the State Department of Health, on which a pharmacist, a physician and a dentist will sit in an advisory capacity, to formulate regulations. What they will do to prevent smuggling of narcotics, or the cultivation of Marihuana in the backyards is not known.

"National First Aid week is scheduled for May 16th to 22nd. This is the 16th annual observance of that week, although not much has ever been done in New York City on account of the strict Health Department Regulations in regard to medical treatment.

"Attention is called to the date of the New York State Pharmaceutical Association's Convention at the Hotel Sagamore, Bolton Landing, June 14th to 18th. Reservations must be made at once as the attendance will be a large one.

"Last Minute Flash! News has just been received that the Twomey Bill Int. 484, print 675 was passed by the Assembly and is now before the Governor for signature. This provides that after July 1, 1937, no pharmacies or drug stores shall be registered by the Board of Pharmacy except if owned by a registered pharmacist, licensed druggist, a person having at least four years' experience in the retail drug business, or registered corporations."

Dr. Hugo Schaefer then reported as secretary of the Remington Honor Medal Committee. Before announcing the name of the recipient he read, among others, the following statements of reasons for the choice. "This man is probably the country's outstanding professional pharmacist. Because of his professional skill and devotion to professional ideals, his name has become synonymous with the best that pharmacy has to offer. In his store, pharmacy is given its finest interpretation and expression. In his professional practice, he has set a pattern which is ideal." Dr. Schaefer announced the recipient to be Dr. J. Leon Lascoff, second vice-president of the A. PH. A. and called on Mrs. J. Leon Lascoff, who was present, for a few words.

Mrs. Lascoff acknowledged the privilege of being permitted to speak and in a few well-chosen words thanked the committee of award and the Branch for the honor bestowed on her husband.

Dr. Lascoff then briefly expressed his thanks to the committee.

There being no further business President Schaefer turned the chair over to Dr. C. P. Wimmer who introduced Dr. Herman Goodman who addressed the meeting on "Allergy to Cosmetics." Dr. Wimmer then introduced Dr. A. J. Frascatti who addressed the meeting on the subject of "Perfume Materials and Perfume Formulation."

At the conclusion, Dr. Wimmer made some pertinent remarks on both talks and requested discussion from the floor. Many members asked questions of the speakers and finally a rising vote of thanks was accorded the speakers and the meeting adjourned.

HORACE T. F. GIVENS, *Secretary*.

NORTHERN NEW JERSEY.

The twenty-ninth regular meeting of the Northern New Jersey Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION, which was held at the Rutgers College of Pharmacy, was the annual joint Pharmacists-Physicians meeting.

Dr. Chester I. Ulmer, chairman of the Committee on Professional Relations of the Medical Society of New Jersey, spoke for the physicians. The counter-prescribing pharmacist and the dispensing physician came in for their round of criticism. He said: "Many of the doctors' offices have become annexes to the advertising departments of the patent medicine industries." "The act of handing the patient a sample of a proprietary medicine is looked upon by the patient as the highest endorsement of the preparation and over the drug counter sales for this product are created."

George C. Schicks, assistant dean of Rutgers College of Pharmacy, spoke for the pharmacists. Mimeographed copies of "Seasonable Prescriptions for Spring and Summer" consisting of suggested prescriptions for the treatment of colds, analgesics, poison ivy, sunburn preventive and treatment, and athlete's foot, were distributed for criticism and comment.

In the dispensing laboratory of the college the students of the upper classes were demon-

strating the compounding of various types of prescriptions and also apparatus for emulsification, capsule filling, etc.

Luncheon was served.

C. L. Cox, *Secretary.*

PHILADELPHIA.

The May meeting of the Philadelphia Branch, AMERICAN PHARMACEUTICAL ASSOCIATION was held on Tuesday evening, May 11th, in the Sullivan Memorial Library of Temple University. The meeting was called to order by Vice-President Kerlin, who presided in the absence of President Kendig.

The minutes of the April meeting were read and approved.

There being no committees reporting, the guest speaker of the evening was introduced. The speaker, Dr. Garfield Duncan of the *diabetic departments* of the Pennsylvania and Jefferson Hospitals discussed the various types of insulin used in diabetic therapy. He discussed particularly the use of protamin-zinc-insulin, pointing out the advantages of this preparation over unmodified insulin.

At the close of Dr. Duncan's discussion some very interesting questions were brought up by Dr. Cobe, Mr. Slavin and Dr. Munch.

ARTHUR K. LEBERKNIGHT, *Secretary.*

COSMETIC PERFUMES—THE RAW MATERIALS, FORMULATION, APPLICATION.*

Cosmetics are no longer a luxury but a necessity. There has been a tremendous advance in compounding of cosmetics and the blending of perfumes. The cosmetic manufacturer is not satisfied with a simple oil as heretofore, but requires the most complex and exotic odors.

A good perfume must fulfil many requirements: it must be compatible with the product in which it is used; it must be harmless dermatologically, that is, it must not irritate, cause blotching, itching, drying nor contain substances known to cause allergic reactions; it must not discolor; it must remain unchanged over long periods of time when stored under different conditions of temperature and it must completely cover the odor of the materials used in the manufacture of the cosmetic.

Factors which operate against the use of essential oils and in favor of synthetics are: the cost of synthetics is usually much less than that of the naturals, the lack of uniformity and the frequent difficulty of obtaining the natural oils is important. The essentials frequently cause discolorations. One of the strongest reasons is fashion. Fashion follows the mode, and the mode requires certain odors that cannot be made without the use of synthetics. The most important factor against natural oils is control. The manufacturer cannot control the essentials. Every shipment is different and he must constantly change his formulas. Synthetics, on the other hand, are made by standard reactions, within practical limits they are always constant in composition and have the same odor value.

In compounding a perfectly perfumed cosmetic, the perfumer must make numerous tests of each ingredient entering his perfume, he must repeat them with his finished perfume and after he is satisfied, the product must be checked by a biochemist to determine whether any harmful effects result when used. Only after long and painstaking experiments and trials will the product be released on the market.

THE ASSOCIATION OF OFFICIAL AGRICULTURAL CHEMISTS AND ITS VALUE TO PHARMACY.[1]

BY L. E. WARREN.

ABSTRACT.

The Association of Official Agricultural Chemists is a group interested in methods for the analysis of agricultural products, such as caustic poisons, fertilizers, food and drugs, insecticides, paints, tanning materials, etc. Its membership consists of chemists employed by the Federal,

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* Abstract of a paper read before the New York Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION at its May 1937 meeting, by Dr. A. T. Frascati, Chief Chemist, Firmenich and Co.

[1] Read before Washington Branch, AMERICAN PHARMACEUTICAL ASSOCIATION.

State, county or city governments in North America. The Association is supported by its publications. It issues two periodicals, the *Journal of the Association*, published quarterly, and "Official and Tentative Methods of Analysis," better known as "Methods of Analysis," revised quinquennially. The Association was founded in 1883, primarily to improve the existing methods for the analysis of fertilizers. Later the Association extended its activities into numerous other fields. It now describes analytical methods and, to a lesser extent, qualitative tests and quantitative standards for about 25 classes of products. The Association endeavors to provide assays for drugs and preparations that have not been admitted to the U. S. Pharmacopœia or National Formulary or are not directed to be assayed by these authorities. The Association also endeavors to find methods for the analysis of mixtures of drugs, and it has devoted a great deal of effort in devising methods for the separation and determination of two or more ingredients in such preparations. Exclusive of microchemical methods, but including the biological procedures, the Association now describes one or more methods for the assay of about 100 drugs or mixtures of drugs. In addition, microchemical methods are given for the detection of 29 alkaloids and 15 synthetic substances. As a rule, the Association is not concerned in establishing standards for drugs.

In addition to the chapter on drugs in the *Book of Methods*, numerous procedures have been adopted by the Association which are designed for the analysis of various products other than drugs but which are applicable in drug analysis. Examples are: The determination of small quantities of metals in foods, such as arsenic, bismuth, copper, lead, mercury, etc.; rapid methods for the determination of aldehyde-free alcohol; a method for the determination of volatile oils in spices which is applicable to such drugs as cinnamon, clove and nutmeg; some of the methods for Baking Powder and Baking Chemicals are adaptable to the assay of Granular Effervescent Salts, a number of which are described in the U. S. P. XI and N. F. VI but only a few are assayed. Nearly every medicinal product that comes to the shelves of the pharmacist is subject to some form of analytical control, either by the manufacturer or by legal agencies. The methods of the Association have been accorded recognition by the Regulations for the enforcement of the Federal Food and Drugs Act where the methods of the U. S. Pharmacopœia and the National Formulary are not applicable. Consequently, the analytical methods for drugs which are worked out by the Association have a very distinct and useful function in the control of drug products. Effectual analytical control insures dependable medicines for the pharmacist and his customers. Every pharmacist in the land receives some measure of protection by the activities of the Association.

STUDENT BRANCH, UNIVERSITY OF SOUTHERN CALIFORNIA.

The Student Branch of the University of Southern California has been presented with the National Charter as Trojan Chapter of the A. PH. A., by Dr. Albert S. Raubenheimer, Dean of the College of Letters, Arts and Sciences. President Harold Miller received the honor on behalf of the Student Branch. The presentation was made at a luncheon; the speakers were Dean Laird Stabler, Professors Harold R. Bowers, Alva G. Hall, Margaret Airston and Willard G. Smith.

The Student Chapter of the National organization has been sponsoring the Pharmaceutical Garden at the University.

Reports on other Branches in next issue of the JOURNAL.

CONFERENCE OF PHARMACEUTICAL ASSOCIATION SECRETARIES.

The officers of the Conference are: *President*, J. W. Slocum, Iowa; *First Vice-President*, Alice E. Garvin, Connecticut; *Second Vice-President*, Robert S. Lehman, New York; *Acting Secretary-Treasurer*, J. Lester Hayman, West Virginia. *Executive Committee:* J. Lester Hayman, West Virginia; W. Irl Brite, Arkansas; F. V. McCullough, Indiana; Otis F. Cook, Michigan.

Messages have been sent to all state associations advising them that the sessions will follow, as far as possible, the program of last year—see February JOURNAL, pages 172–189. If you have not received the *Bulletin*, address Lester J. Hayman, 325 Ash St., Morgantown, W. Va. Parts of the following paragraphs are quoted:

"As is generally known, our meetings are held in conjunction with those of the AMERICAN PHARMACEUTICAL ASSOCIATION, with which we are affiliated. The meeting will be held

in New York City during the week of August 16th, at the Pennsylvania Hotel. It is hoped that we may have a good representation of secretaries in attendance. In the enclosed reprint of the Proceedings of the last meeting, our deceased secretary says, 'I am perfectly sincere when I make the assertion that a state association can make no better investment of a small part of its funds than by sending its secretary to these conferences where he may study at first hand practical ideas of his secretarial confrères and at the same time, perhaps, give them the benefit of his own experience—all for the ultimate good of association activities.' To those of us who have had the opportunity of attending these Conferences, the meeting is worth many times the cost.

"May we ask each secretary receiving this bulletin to contact President Slocum as soon as possible and inform him as to whether or not you think you can or will attend the New York meetings. We also ask those who seem to think they cannot attend to give that information, too, together with the reason why. This information is desired so that we may contact the proper persons of your organization to ascertain whether or not they cannot pay all or part of your expenses. We will be glad to do this for you so that you can assist us."

J. W. SLOCUM, *President.* J. LESTER HAYMAN, *Acting Secretary.*

TENTATIVE PROGRAM FOR THE PLANT SCIENCE SEMINAR.

Accommodations have been arranged for the group in West Philadelphia; Headquarters, Philadelphia College of Pharmacy and Science.

MONDAY, AUGUST 9th.

1:00 P.M. Registration.
2:30 P.M. Field trip to Bartram's Garden.
7:00 P.M. Fel's Planatarium, after which a trip to downtown Philadelphia.

TUESDAY, AUGUST 10TH.

8:30 A.M. Field trip to Fairmount Park, Morris Arboretum and Horticultural Hall.
2:30 P.M. Business Meeting.
Reading of Papers.
Inspection of Kilmer's Garden.
8:30 P.M. A speaker, to be decided later.
Moving pictures of former Seminars.

WEDNESDAY, AUGUST 11TH.

7:30 A.M. Leave for Vineland, N. J. (Headquarters).
Dr. Newcomb will have the Seminar as his guests for a boat trip, collecting down the Maurice River. A picnic dinner at Millville.

THURSDAY, AUGUST 12TH.

Excursions to silica plants, glass plants, textile mills and rayon factory.

FRIDAY, AUGUST 13TH.

Logansport, N. J., sea and seashore collecting. Shore dinner in the evening.

Group at last year's Plant Science Seminar meeting, Oklahoma.

ASSOCIATION BUSINESS

AD INTERIM BUSINESS OF THE COUNCIL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, 1936–1937.

Office of the Secretary, 2215 Constitution Avenue, Washington, D. C.

LETTER NO. 13.

May 18, 1937.

To the Members of the Council:

95. Use of Text of N. F. VI. Motion No. 43 (Council Letter No. 12, page 451) has been carried and Lea & Febiger have been so advised.

The following communication has been received from Chairman DuMez of the Committee on Publications:

"Dr. Robert Fischelis has requested to use the titles of certain N. F. VI preparations in 'The New Jersey Formulary' which is to be published soon under the auspices of the New Jersey Pharmaceutical Association in coöperation with the Medical Society of New Jersey.

"I have looked over the manuscript carefully and do not find the use of N. F. titles to be unduly extensive or objectionable in other ways. I therefore recommend that permission to use the N. F. for comment as indicated be granted and that no fee be charged for the grant."

(*Motion No. 47*) It is moved by DuMez that Dr. Robert P. Fischelis be granted permission to use the titles of certain N. F. VI preparations in an early edition of "The New Jersey Formulary" with the customary acknowledgment and for value received.

96. Corrections in N. F. VI. Motion No. 44 (Council Letter No. 12, page 452) has been carried with Dr. Fischelis recorded as not voting.

15,000 copies of Corrections in N. F. VI (Second List) have been ordered from the Mack Printing Company with the following changes in the proof (sent with Council Letter No. 12) as requested by Chairman Gathercoal: On page 4, Kamala, the seventy per cent of non-volatile ether-soluble extractive matter, has been reduced to sixty-six per cent; on page 6, the alcohol percentage of Tincture of Vanilla has been changed from "37 to 41" to "40 to 44."

The bulletin quoted in Council Letter No. 12 will be sent to the publications mentioned as soon as the Corrections in N. F. VI (Second List) are ready for distribution.

97. Election of Members. Motion No. 45 (Council Letter No. 12, page 452) has been carried and applicants for membership numbered 318 to 326, inclusive, are declared elected.

98. Investment of Funds. Motion No. 46 (Council Letter No. 12, page 453) received a majority of votes with Dr. Fischelis recorded as not voting, and with Dr. Dunning voting no with respect to the sale of the bonds enumerated in Group 1 on page 452, on account of the changed conditions, and yes with respect to the investment of the funds on hand.

With the best advice obtainable, it seemed advisable to proceed with the investment of the funds on hand amounting to $40,000.00, in the U. S. Treasury Bonds, 2¾%, 1956–1959, which was done on a 2.77% basis, and to retain the bonds enumerated in Group 1 for the present at least. If there is an important change with respect to the latter, a recommendation will be submitted to the Council.

99. *Applicants for Membership.* The following applications, properly endorsed and accompanied with the first year's dues, have been received:

No. 327, Albert E. Chase, 102 W. 4th St., Santa Ana, Calif.; No. 328, V. L. Roberson, Sherwood Petroleum Co., Bush Terminal No. 1, Brooklyn, N. Y.; No. 329, Samuel S. Kovacs, 2632 S. Dearborn St., Chicago, Ill.; No. 330, Charles P. Leahy, 8830 Betty Way, Los Angeles, Calif.; No. 331, Robert C. Gibbs, 220 E. Gray St., Louisville, Ky.; No. 332, Warren P. Boulton, State Capitol, Frankfort, Ky.; No. 333, Leo K. Mills, Jr., 1000 E. 4th St., Owensboro, Ky.; No. 334, George E. S. Wilson, 4605 So. 6th St., Louisville, Ky.; No. 335, John Geo. Krul, 2763 Grinstead Drive, Louisville, Ky.; No. 336, Harry J. Lichtefeld, 400 E. Ormsby, Louisville, Ky.; No. 337, Peter A. Weber, 335 S. Preston, Louisville, Ky.; No. 338, James E. Paris, 119 W. Court, Paragould, Ark.; No. 339, James R. Oliver, 800 E. 13th, Oklahoma City, Okla.; No. 340, Roy L. Crouch, R. F. D. No. 2, Roanoke, Va.; No. 341, Noel Moore Ferguson, St. Louis College of Pharmacy, St. Louis, Mo.; No. 342, Isadore Seldin, 1604 Park Rd., N. W., Washington, D. C.;

No. 343, Theodore E. Caruso, 141 E. 88th St., New York, N. Y.; No. 344, Roy G. Paulson, Fairmont, Minn.; No. 345, David Waldinger, 56 Beech St., Belleville, N. J.; No. 346, Paul W. Snyder, 1002—9th St., Greeley, Colo.; No. 347, Robert A. Hardt, 745 Fifth Ave., New York, N. Y.; No. 348, Anthony J. Monte-Bovi, St. John's University, Brooklyn, N. Y.; No. 349, Paul E. Tullar, 250 Mamaroneck Ave., White Plains, N. Y.; No. 350, Manuel F. Raubfogel, 209 Bridge St., Phoenixville, Penna.; No. 351, Willis J. Heyl, 342 E. 26th St., Erie, Pa.; No. 352, E. Catherine Blumenschein, 27 W. Main St., Uniontown, Pa.; No. 353, Cecil B. Rebert, 344 Lincoln Ave., Bellevue, Pa.; No. 354, Thomas J. Duda, R. D. 10, Box 21, Crafton Br., Pa.; No. 355, Italo Alfred Bianculli, 1407 Grotto St., Pittsburgh, Pa.; No. 356, Victor H. Shepherd, 412 Covitt Ave., Trafford, Pa.; No. 357, Philip P. Dosch, 772 N. Center Ave., Somerset, Pa.; No. 358, Paul G. Hawkins, Fredericktown, Pa.; No. 359, James W. Shaver, 626 Air Brake Ave., Wilmerding, Pa.; No. 360, Thomas G. Jaffe, 1751 Seward Ave., New York, N. Y.; No. 361, Alfred J. White, 80–83 Tryon Rd., Jamaica Estates, L. I., N. Y.; No. 362, Frederick L. Geiler, 341 Dorsey Ave., Morgantown, W. Va.; No. 363, Clark Crane, 2946 California St., Huntington, Calif.; No. 364, Weldon R. Rechburg, 3100 W. 25th St., Cleveland, Ohio; No. 365, Douglass B. Pew, 3670 E. 163d St., Cleveland, Ohio; No. 366, Charles V. Selby, 220 Milford St., Clarksburg, W. Va.; No. 367, Maurice Schuman, 443 Broadway, New York, N. Y.; No. 368, J. J. Vazquez, Pedro Moreno No. 1470, Guadalajara, Mexico; No. 369, Bernard Leon Zenitz, 3800 Towanda Ave., Baltimore, Md.; No. 370, Shuko Yoshihara, 101 Whitman St., Pullman, Wash.; No. 371, Jeptha Wilson Wille, 2603 Guadalupe St., Austin, Texas; No. 372, Harold A. Vaubel, 108 Madison Park Terrace Ave., Peoria, Ill.; No. 373, Andre Girardet, Ecole de Pharmacie, University of Lausanne, Switzerland.

(*Motion No. 48*) Vote on applications for membership in the AMERICAN PHARMACEUTICAL ASSOCIATION.

100. American Society for Testing Materials. The following letter was received from Mr. C. L. Warwick, Secretary-Treasurer of the Society:

"On behalf of the Executive Committee of the Society I am pleased to extend an invitation to your association to become a member of the Society and to serve on a committee that we are about to organize, to be known as Committee C-14 on Glass and Glass Products. The scope of the committee will comprise the development of nomenclature and methods of analysis and testing of glass, both as such and as specific products. The committee is being organized at the suggestion of the Glass Division of the American Ceramic Society, to provide, in accordance with long established procedures of the American Society for Testing Materials, the opportunity of bringing together producers, consumers and general interests for the purpose of developing American standards for the testing of glass and glass products.

"It is planned that the work of the committee initially will deal, through appropriate sub-committees, with such matters as (1) nomenclature and definitions; (2) methods of chemical analyses of glass; (3) chemical properties of glass, including durability; (4) physical and mechanical properties; and (5) thermal properties. The request has been made that the new committee give consideration to the testing of one glass product, namely, glass construction blocks, and provision is being made for the formation of a sub-committee on this subject. Consideration of tests for electrical properties of glass will remain in the hands of the Society's Committee D-9 on Electrical Insulating Materials, where such work has been under way for some little time.

"Membership in the Society is required for eligibility to serve as a member of an A. S. T. M. committee. I presume that you are informed in at least a general way about the Society. The accompanying booklet on 'Purpose and Work' will tell you more about us and the list of standards and publications will show both the nature and diversification of the fields in which we are engaged. We believe that your association will have a real interest in this work, especially, of course, as it pertains to the development of standards concerning glass containers used in the pharmaceutical field and we should be pleased to learn that you are interested and desire to become affiliated with us. If so, may I suggest that you fill out the application form enclosed; there will be no need under the circumstances to obtain any endorsing signatures.

"I sincerely trust that your association will wish to participate in this work and I assure you we shall welcome your coöperation. The Executive Committee of the Society has designated Dr. G. W. Morey, Geophysical Laboratory, Washington, D. C., as temporary chairman of the new committee, charging him with the responsibility of organizing the committee. As soon

as the acceptances have been received from those to whom this invitation is being extended, Doctor Morey will determine the date of and arrange for the organization meeting of the committee."

The letter was referred to President Beal who wrote as follows:

"I am returning herewith the letter from Mr. C. L. Warwick, Secretary-Treasurer of the American Society for Testing Materials. I should like to move that the Council authorize the participation of the AMERICAN PHARMACEUTICAL ASSOCIATION in this work at a cost for the first year of $40.00 and thereafter $30.00 annually, said fees to be charged against the National Formulary revision account.

"Having participated in some of the discussions that led to the reception of this plan on the part of the A. S. T. M. and having discussed it still more fully with the members of the Division of Glass Technology of the American Ceramic Society, I am convinced that this is an activity in which the AMERICAN PHARMACEUTICAL ASSOCIATION ought, by all means, to participate. The ASSOCIATION has made a good start on this problem but we have been limited by the fact that we have no glass technologists in our group and that our most crying need was for improved standards for ampul glass. This committee hopes to effect a thorough standardization of glass containers of all types with particular attention to chemical resistance and in many instances the effect of color upon preservation. The results of the committee work should eventually lead to specifications that may well be adopted by the National Formulary and the U. S. Pharmacopœia, and under such circumstances I think that it would be a mistake for the ASSOCIATION to fail to participate."

Chairman Gathercoal of the Committee on National Formulary has given his approval to the proposal and the membership fee of $40.00 will be charged to the appropriation for the N. F. already included in the 1937 budget. Chairman Swain of the Committee on Finance has approved this arrangement.

(*Motion No. 49*) It is moved by George D. Beal that the membership of the A. PH. A. in the American Society of Testing Materials at a cost of $40.00 for the first year and $30.00 thereafter, be approved, and that the president be authorized to appoint a representative of the A. PH. A. to serve on Committee C-14 on Glass and Glass Products of the Society.

A vote is called for at this time as it is desired to have an early meeting of the committee, and will be considered tentative if there is objection or if members of the Council desire to submit comments.

E. F. KELLY, *Secretary.*

TEMPLE SCHOOL OF PHARMACY AWARD.

With appropriate ceremonies, the presentation of the award to Temple University by the AMERICAN PHARMACEUTICAL ASSOCIATION for the best professional display in the National Pharmacy Week School of Pharmacy competition was made at the Temple School of Pharmacy on May 7th. The exercises took place in the upper amphitheater of the school.

The program was opened by Dean H. Evert Kendig, who extended greetings to the assembled guests. Following Dr. Kendig's welcome, brief addresses were made by Neal B. Bowman, President of the General Alumni Association, and Assistant Professor of Economics and Commercial Pharmacy in the Temple School of Pharmacy, who represented Dr. Charles E. Beury, president of the university; Charles T. Pickett, Secretary of the Philadelphia Association of Retail Druggists; Nathan Zonies, vice-president of the Pennsylvania Pharmaceutical Association; and Robert L. Swain, former President of the AMERICAN PHARMACEUTICAL ASSOCIATION.

The address and presentation of the award—a blue and gold banner, bearing the inscription, "A. PH. A. 1936 Pharmacy Week Display Award, Won by Temple University School of Pharmacy"—was made by Anton Hogstad, Jr., Chairman of the National Pharmacy Committee of the AMERICAN PHARMACEUTICAL ASSOCIATION. The award was formally received by Dean Kendig, after which John A. Lynch, Instructor in Display at the School, presented a model of the display to Chairman Hogstad for the museum of the AMERICAN PHARMACEUTICAL ASSOCIATION.

EDITORIAL NOTES

S. L. Hilton has donated an Analytical Balance to the AMERICAN PHARMACEUTICAL ASSOCIATION. The Balance was manufactured by Voland & Sons, New Rochelle, N. Y.

James G. Carstater, of Oneida, N. Y., has sent a series of snapshots taken during his visit in Washington.

The AMERICAN PHARMACEUTICAL ASSOCIATION has received, through the kindness of Doctor Wm. A. Hamor, of the Mellon Institute of Research, photographs of the emblems relating to the A. PH. A.

Fred. W. Connolly, Dorchester, Mass., has donated to the museum of the AMERICAN INSTITUTE OF PHARMACY five drug jars labeled in rose and gold and three old bottles for drugs, these probably date back to the 15th century. The donor sets an example for others to follow; he has heretofore made other donations.

SECTION ON PRACTICAL PHARMACY AND DISPENSING.

The officers of the Section on Practical Pharmacy and Dispensing solicit the continued interest and coöperation of the members that have made these Section meetings so appealing in past years. Members of the ASSOCIATION are requested to send in their papers at an early date, noting the following requirements:

Please advise the secretary whether the paper will be presented in person or read by title.

The author should follow the procedure outlined in the April 1937 number of the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, outlining Notice to Contributors.

Papers should be presented in duplicate so that one copy will be made available for publication.

The Secretary is Leon W. Richards, State University of Montana, Missoula, Mont.

PART OF TENTATIVE PROGRAM OF SECTION ON COMMERCIAL INTERESTS.

1. "Must a Pharmacist Be a Psychologist?" Alice-Esther Garvin.
2. "The Place of the Professional Display in the Store Program," M. Medford Cooper.
3. "Fair Trade—Past, Present," Samuel Shkolnik.
4. (Title Not Yet chosen), John N. McDonnell.
5. "A Study in Commercial Pharmacy" (Tentative), Neal Bowman.
6. (No Title Given), Charles H. Stocking.
7. (Title Not Yet Chosen), George F. Archambault.
8. (Title Not Yet Chosen), Joseph H. Goodness.
9. "On Twenty-Five Cigar Counters," Walter M. Chase.

PERTINENT SUBJECTS FOR DISCUSSION AT THE CONFERENCE OF PHARMACEUTICAL ASSOCIATION SECRETARIES.

BY J. W. SLOCUM, PRESIDENT, CONFERENCE OF STATE PHARMACEUTICAL ASSOCIATION SECRETARIES.

1. What fields of endeavor should the State Association enter other than legislative?
2. Do you hold mid-winter meetings? District meetings?
3. Should the Conference provide a Bulletin at stated intervals?
4. Has the Washington Bulletin been adequate and satisfactory?
5. What has been the one large accomplishment of your Association during the past year?
6. Should the Conference provide for and hold a meeting at the time of the N. A. R. D. Convention?
7. What success do you have in the collection of dues?
8. Do you operate a drug show in connection with your State Convention?
9. Do you have a Fair Trade Act and how is it working?
10. Are you satisfied with the manner in which you finance the operation of the Act?
11. Are you sure that the Presidential delay of the Tydings Bill will not seriously interfere with the operation of your State Act?
12. How do you propose to operate in the event the Tydings-Miller Bill is delayed indefinitely?
13. What is the real reason why many independent retail druggists in many states, refuse to sign Fair Trade Contracts and give full coöperation?
14. Are manufacturers justified in refusing to make or establish higher minimums in

some states than in others, or are they justified in the claim that minimum schedules should be uniform in all Fair Trade States?

NEW BUILDING OF THE BRITISH PHARMACEUTICAL SOCIETY.

The British Pharmaceutical Society is presenting the architect's plan for the New Building, which the Society will occupy in Brunswick Square, London. The site on which the Society's new house will be erected is the North side of Brunswick Square. The property was acquired by the Society in 1930 and has a main frontage to Brunswick Square of 237 feet and a minor frontage to Hunter St., of 113 feet. The Building will also face St. George's Gardens. It will have seven floors. Opportunity is taken to congratulate the Society and extend best wishes.

OLD POISON LAWS OF FRANCE.

The Revenue d'Histoire de la Pharmacie for March 1937, reproduces the text of a decree of February 27, 1677, governing the distribution of poisons in France. Several of the regulations are quoted.

"Apothecaries and grocers shall keep in a safe receptacle, of which the key shall be in their sole possession, every drug, such as arsenic, sublimate, realgar and similar substances, capable of being employed for the destruction of the human body. It shall not be lawful for a person to sell or supply any such substance unless the purchaser is resident in the neighborhood and known to the seller."

"Every apothecary and grocer shall keep in a form approved by the senior Commissaire du quartier, the names of those persons to whom such substances have been sold or supplied, together with the amount and description, the date and the purpose for which they are required. The purchaser shall affix his signature to the entry."

CINCHONA TREES IN THE PHILIPPINES.

For many years the Dutch have held a virtual monopoly on the growth of cinchona trees. Years ago, Arthur Fischer, head of the Philippine Bureau of Forestry, became interested in the problem of growing cinchona trees in the Philippine Islands. After prolonged investigation a cinchona nursery was started at Impalutau, Bukidnon and Mindanao. At present 5000 acres are being utilized for this purpose. There are now being harvested sufficient amounts of quinine in the form of total alkaloids to meet the requirements of the Philippines. There is still much to be done in the erection of extraction plants in order to place the industry on a commercial basis.

ANNUAL MEETING OF THE COUNCIL ON PHARMACY AND CHEMISTRY.

The following attended the annual meeting of the Council on Pharmacy and Chemistry of the American Medical Association: Dr. David Barr, Dr. J. Howard Brosn, Dr. S. W. Clausen, Dr. H. N. Cole, Dr. C. W. Edmunds, Dr. Morris Fishbein, Dr. Paul Nicholas Leech, Dr. G. W. McCoy, Dr. E. M. Nelson, Dr. W. W. Palmer, Dr. William C. Rose; Dr. James S. McLester, member of the Council on Foods, and Dr. Olin West, General Manager, were also present.

Dr. Torald Sollmann was reëlected chairman of the Council and Dr. W. W. Palmer was reëlected vice-chairman, and Dr. Paul Nicholas Leech, secretary.

NEW AND NONOFFICIAL REMEDIES.

THE FOLLOWING ADDITIONAL ARTICLES HAVE BEEN ACCEPTED AS CONFORMING TO THE RULES OF THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION FOR ADMISSION TO NEW AND NONOFFICIAL REMEDIES. A COPY OF THE RULES ON WHICH THE COUNCIL BASES ITS ACTION WILL BE SENT ON APPLICATION.—PAUL NICHOLAS LEECH, *Secretary.*

NOVATROPINE.—Homatropinemethylbromide.—$C_{16}H_{21}O_3N.CH_3Br$.—The methylbromide of the alkaloid homatropine.

Actions and Uses.—Novatropine is proposed for use in the treatment of gastro-intestinal spasm and hyperchlorhydria. Animal experimentation has shown it to be less active than atropine but also less toxic.

Dosage.—Adults: one or two tablets three times daily before meals; children and infants: according to age.

Manufactured by Campbell Products, Inc., New York. No U. S. patent. U. S. trademark 240,537.

Novatropine Tablets, 1/24 grain: Each tablet contains 1/24 grain (2.5 mg.) homatropinemethylbromide.

Novatropine occurs as an odorless, white, crystalline powder, possessing a bitter taste, soluble in water and alcohol but insoluble in ether. It melts between 191 and 192 C., with slight decomposition. Aqueous solutions (1 in 50) are neutral to litmus.

For distinction from atropine, hyoscyamine and scopolamine—see *Journal A. M. A.*, April 10, 1937, page 1259; also, *distinction from homatropine, hydrobromide, atropine and hyoscyamine.* See also method described in "Methods of Analysis of the Association of Official Agricultural Chemists," fourth edition, page 23, art. 19, and method described in "Methods of Analysis of the Association of Official Agricultural Chemists," fourth edition, page 131, art. 55.

PAPAVERINE HYDROCHLORIDE (See New and Nonofficial Remedies, 1936, p. 321).

Papaverine Hydrochloride-Mallinckrodt.—A brand of papaverine hydrochloride-N. F.

Manufactured by Mallinckrodt Chemical Works, St. Louis.

OPTOCHIN HYDROCHLORIDE.—$C_{12}H_{22}N_2OH.O.C_2H_5HCl$.—The hydrochloride of ethylhydrocupreine.

Actions and Uses.—See general article, Ethylhydrocupreine, N. N. R., 1936, p. 216.

Dosage.—For application to the eye and instillation into the conjunctival sac, a freshly prepared 1 or 2 per cent solution is used. It is not recommended for oral administration.

For standards see the U. S. Pharmacopeia under Æthylhydrocupreinæ Hydrochloridum.

Tablets Optochin Hydrochloride, 0.1 Gm.

Manufactured by Rare Chemicals, Inc., Nepera Park, N. Y., under U. S. patent 1,062,203 (May 20, 1913; expired) by license of the Chemical Foundation Inc. U. S. trademark 99,822.

DIGITALIS (See New and Nonofficial Remedies, 1936, p. 168).

The following dosage forms have been accepted:

Tablets Digitalis Duo-Test McNeil, 1/2 grain: Each tablet contains 1/2 cat unit.

Tablets Digitalis Duo-Test McNeil, 1 grain: Each tablet contains 2/3 cat unit and is dispensed in plain and enteric coated tablets. The enteric coated tablets are first coated with a wax-salol mixture and then sugar coated green.

Tablets Digitalis Duo-Test McNeil, 1 1/2 grains: Each tablet contains 1 cat unit and is dispensed in plain and enteric coated tablets. The enteric coated tablets are first coated with a wax-salol mixture and then sugar coated green.

Capsules Digitalis Duo-Test McNeil, 1 1/2 grains: Each capsule contains 1 cat unit and is dispensed in black capsules.

Prepared by the McNeil Laboratories, Inc., Philadelphia.

DIPHTHERIA TOXOID, ALUM PRECIPITATED (REFINED) (See New and Nonofficial Remedies, 1936, p. 392).

Mulford Biological Laboratories, Sharp & Dohme, Philadelphia and Baltimore.

Diphtheria Toxoid, Alum Precipitated.—Prepared by treating diphtheria toxoid with a solution of alum until complete precipitation is produced. The precipitate is thoroughly washed and then suspended in physiologic solution of sodium chloride. The product is tested for antigenic potency according to the method prescribed by the National Institute of Health: guinea-pigs weighing 500 Gm., given one human dose, must produce at the end of six weeks at least two units of diphtheria antitoxin in each cubic centimeter of blood. Ortho-chloro-mercuri phenol 1:20,000 is used as the preservative.

Marketed in packages of one 0.5 cc. vial and one 1 cc. vial; in packages of ten 0.5 cc. vials and ten 1 cc. vials; and in packages of one 5 cc. vial and one 10 cc. vial.

AMINOPYRINE (See New and Nonofficial Remedies, 1936, p. 340).

Aminopyrine-"National."—A brand of aminopyrine-U. S. P.

Manufactured by the National Aniline and Chemical Co., New York.

Aminopyrine Tablets, 5 grains.

COD LIVER OIL (See New and Nonofficial Remedies, 1936, p. 450).

Möller Plain Cod Liver Oil Standardized.—It has a vitamin A potency of not less than 1,000 units (U. S. P.) per gram and a vitamin D potency of not less than 150 units (U. S. P.) per gram.

Dosage.—For adults, 4 cc. (60 minims) to 15 cc. (225 minims) three times a day; for children, 2 cc. (30 minims) to 4 cc. (60 minims) three times a day.

Manufactured by Peter Möller, A/S, Oslo, Norway; distributed in the United States by Schieffelin & Co., New York. No U. S. patent or trademark.

Möller plain cod liver oil standardized complies with the U. S. P. standards for cod liver oil. In addition it is required to have a vitamin. A potency of not less than 1,000 units per gram and a vitamin D potency of not less than 150 units per gram.—*J. A. M. A.*, April 24th, page 1410.

PERSONAL AND NEWS ITEMS.

President A. C. Taylor, of the District of Columbia Board of Pharmacy, has been quite ill for some time but is improving. It was necessary for him to go to the hospital but he is now at home.

R. L. Swain addressed the Independent Retail Food Dealers in Maryland at Hotel Emerson on the subject, "The Public Health Significance of Drugs and Medicines."

Charles T. Heller was honored at the meeting of the Minnesota Pharmaceutical Association by tribute to the service in pharmacy during fifty years of pharmaceutical activity in Minnesota.

Among the speakers at the South Dakota meeting of the State Pharmaceutical Association were: **Rowland Jones, Jr., Frank Mortenson,** Governor Leslie Jensen and Dean E. R. Serles.

Among the get-together affairs of the meeting were, The Veterans' Banquet and the Rho Chi Breakfast. The Chairman is H. A. K. Whitney, University Hospital, Ann Arbor, Mich.

He addressed the dentists of Bay County, Michigan, on May 17th. His subject was, "Analgesics."

President Wilmer Krusen, of the Philadelphia College of Pharmacy and Science, was honored at a Birthday Dinner on May 26th, upon the completion of ten years as president of the college. The dinner was attended by representatives of government, education, religion, law and science. Among the speakers were: Mayor Wilson, Josiah H. Penniman, provost of the University of Pennsylvania, and members of the faculty. An oil portrait was presented to Dr. Krusen.

A testimonial dinner was tendered to **Dean William Christine Anderson,** of the Brooklyn College of Pharmacy, Long Island University, on June 1st, at the Towers, Brooklyn, N. Y.

Dr. Anderson is succeeded as dean by **Dr. Hugo H. Schaefer.** The former retains his connection with the college as **Dean Emeritus.** More than 300 guests attended the enjoyable occasion; among them were representatives of schools, state and national associations. Dr. and Mrs. Anderson rarely miss the annual meetings of the AMERICAN PHARMACEUTICAL ASSOCIATION; congratulations and good wishes are extended to them.

Dr. Leon Richards, associate professor in pharmacy, will spend his summer vacation in doing research work for the United States Forest Service in the vicinity of Priest River, Idaho.

A testimonial dinner was given for **John F. Walsh,** by Massachusetts druggists on April 6th. Mr. Walsh, recently reappointed to the Massachusetts Board of Pharmacy, is its president. He is also first vice-president of the National Association of Boards of Pharmacy.

Miss Jessie M. Porter, Rockford, Ill., emphasizes her prescription department, which is up-to-the instant in appearance and operation. She is 70 years of age—the third graduate of Northwestern College of Pharmacy.

The Warner Drug Co., El Paso, Texas, has a fully equipped woodcraft shop, operated by a full-time employee and an assistant. Here are produced all display material, including signs, cases and model stock exhibits.

Climaxing National First Aid Week, the president of the N. A. R. D., **Dr. George L. Secord,** was precipitated into a series of events which served to emphasize indelibly the need for more wide-spread knowledge of first aid principles. Newspaper accounts of a wreck, while minimizing the number of injured, credited President Secord for his thoughtfulness in rendering first aid in the emergency.

Ernest I. Kilcup, Managing Executive of the Davol Rubber Company, Providence, R. I., has received the honorary degree of Doctor of Science from the Rhode Island College of Pharmacy, June 9th.

The award is made in recognition of Mr. Kilcup's services as an executive and honorary officer of the National Association of Credit Men as well as his services in the pharmaceutical field. The exact wording includes the sentence "For distinguished service to the community and for his contribution to the welfare of the pharmaceutical trade."

W. C. Powell became a member of the Maryland Board of Pharmacy in 1902 and is now succeeded by **L. D. Johnson** of St. Michaels. Recognition will be given at the Maryland Pharmaceutical Association at Ocean City to the retiring member of the Board, Wm. C. Powell.

The Louisiana State Museum, located at New Orleans, issues a *bulletin* periodically. A number that has come to our hands is entitled, "Glamorous Louisiana under Ten Flags." The first is that of Spain; the second of France; and successively of France, Spain, England, France, United States, the Lone Star, Louisiana, Confederate States and Louisiana State Flag.

Commander Roddis, who has been editor of the *United States Naval Medical Bulletin* for the past four years, and assistant editor of the *Military Surgeon*, has been ordered to duty as executive officer of the Naval Hospital at Honolulu. He is well known to many members of the ASSOCIATION and also widely known as a medical and pharmaceutical historian, and has been a frequent contributor on these subjects to the *Military Surgeon* and has contributed a number of articles to the Section on Historical Pharmacy, A. PH. A.

Dr. L. O. Howard was honored on his 80th birthday by fellow scientists and members of the Entomological Society, of Washington.

DEAN H. V. ARNY HONORED.

Dean Henry V. Arny of the College of Pharmacy of Columbia University was the guest of the teaching staff and administrative officers at an informal luncheon, May 21st. The gathering was intended as a personal testimonial by those who have been associated with Dean Arny during his twenty-five years' service at the College. Professors Wimmer and Ballard, in speaking, expressed the hope that, although relieved of routine duties, Dr. Arny would still be active in College affairs. Professor Brown, on behalf of those attending, presented Dr. Arny with a gift as a tribute from his co-workers in the College.

The Dean was president of the AMERICAN PHARMACEUTICAL ASSOCIATION, 1923-1924.

Dean A. R. Bliss, of the School of Pharmacy, of Howard College, Birmingham, was one of the principal speakers at the meeting of the Alabama Pharmaceutical Association held in Montgomery.

NEW YORK A. PH. A. MEETINGS.

The 1855 meeting of the ASSOCIATION was presided over by **John Meakim.** He was a native of New York City. In his earlier years he was engaged in New York City Dispensary. In 1836 he graduated from New York College of Pharmacy, was engaged with Rushton and Aspinwall until 1840, when he established a pharmacy on his own account.

Henry Kiersted was a native of New York City. He entered pharmacy in 1814 and, later, established his own pharmacy. Mr. Kiersted was one of the founders of New York College of Pharmacy and for a number of years its president.

John Milhau was a native of Baltimore. He studied pharmacy in Paris. Soon after settling in New York, he established a pharmacy and became identified with New York College of Pharmacy and held official positions with that institution for many years.

William M. Searby presided at the 1907 meeting in New York City. For many years he was identified with pharmacy of the Pacific Coast, as retail pharmacist, member of the pharmacy faculty, San Francisco, and as editor of the *Pacific Pharmacist*.

The selection of **Dr. Charles W. Ballard,** professor of Materia Medica in the College of Pharmacy, Columbia University, as the new dean of the college, has been officially announced by Dr. Nicholas Murray Butler, president of the University. He will succeed **Dean Henry V. Arny,** whose retirement becomes effective July 1st.

Dr. Ballard has been associated with the Columbia College of Pharmacy for thirty years. Since 1917, he has been connected with the New York City Health Department as a drug and food analyst.

On account of health conditions, **Dean Charles F. Heebner,** after forty-six years' service to the Ontario College of Pharmacy, has found it necessary to resign as Dean of the faculty. References to Dean Heebner were made in the March and in the April JOURNALS. He became a member of the AMERICAN PHARMACEUTICAL ASSOCIATION in 1894. Good wishes are extended for improved health.

The following received Honorary Degrees in Pharmacy from the Philadelphia College of Pharmacy and Science, on June 9th: **President Frederick Blumenschein,** of the Pennsylvania State Board of Pharmacy; **Ralph R. Foran,** Chief Control Chemist of Merck & Co.; **Prof. Harvey Frank,** of the College Faculty; **Secretary Paul N. Leech,** of the Council on Pharmacy and Chemistry, American Medical Association. The latter delivered the commencement address to the graduating classes; seventy-two degrees were conferred upon students. Degrees this year were granted in bacteriology, biology, chemistry and pharmacy.

Pharmacist William Gray has been active in the AMERICAN PHARMACEUTICAL ASSOCIATION since 1892. He is shown in the May *Bulletin* of the Presbyterian Hospital of the City of Chicago, with members of the Pharmacy staff.

Prof. Ralph W. Clark, who was a member of the faculty of University of North Carolina School of Pharmacy during the past year, has returned to Wisconsin. Accompanied by Mrs. Clark and children, Professor Clark visited the AMERICAN INSTITUTE OF PHARMACY on his return; he also attended the convention of West Virginia Pharmaceutical Association.

Heinrich Martens, Sheboygan, Wisconsin, is visiting in Germany. He expects to attend functions of pharmaceutical organizations during his stay of several months.

Governor Charles F. Hurley, of Massachusetts, was one of the principal speakers at the annual banquet of Massachusetts Pharmaceutical Association, at Swampscott.

C. Jelleff Carr, of the Department of Pharmacology, School of Medicine, University of Maryland, received the degree of Doctor of Philosophy at College Park on Saturday, June 5th.

William F. Reindollar, chief, Bureau of Chemistry, State Department of Health, was awarded the degree of Doctor of Science in Hygiene by the Johns Hopkins University at the commencement held in Baltimore on Monday, June 7th.

George A. Bunting, a member of the class of 1891 at Washington College, Chestertown, Md., has made a contribution of $50,000.00 toward the erection of a modern library building for the college.

"The old apothecary shop," of Revolutionary days, was arranged by the Pharmacy Department of the Medical College of Virginia and is a prominent feature of the exhibit. "Two Hundred Years in Medical Progress" is part of the Virginia Capital Bicentennial Commission's celebration of the founding of Richmond.

SOCIETIES AND COLLEGES.

UNIVERSITY OF MARYLAND.

The alumni of the School of Pharmacy of the University of Maryland held their annual banquet on June 3rd, at Lord Baltimore Hotel. President John A. Wannenwetsch presided and R. L. Swain discharged the duties of toastmaster; Frank J. Slama and John A. Strevig were ably assisted in the entertainment program.

Among the speakers were Hon. W. H. Blakeman, State Budget Director, representing Governor Harry W. Nice, President H. C. Byrd, of the University, and President Gilbert W. Mead, of Washington College, was the principal speaker. Other speakers, besides those mentioned, gave brief talks; among them, Secretary E. F. Kelly, of the A. PH. A., and representatives of classes and organizations. Dean A. G. DuMez awarded the honors.

The commencement exercises were held June 5th at College Park, at which time diplomas and honors were awarded. U. S. Senator Millard E. Tydings delivered the address of the day.

The Gold Medal for General Excellence was awarded to Bernard Leon Zenitz; the L. S. Williams Practical Pharmacy Prize to Frank Joseph Lieb.

FORDHAM COLLEGE COMPLETES "PHARMACY OF THE FUTURE."

The Fordham University College of Pharmacy, New York, has completed its model "Pharmacy of the Future," under direction of **Dr. Otto F. A. Canis.** Formal dedication of the new unit took place on June 9th.

COLLEGE OF PHARMACY OF COLUMBIA UNIVERSITY.

Dean H. V. Arny's resignation has necessitated a reorganization of the Department of Chemistry in Columbia University. Dr. Hugo Schaefer leaves to take the deanship of the College of Pharmacy of Long Island University (Brooklyn College of Pharmacy). Dr. Charles W. Ballard succeeds Dr. H. V. Arny as dean. Dr. Arthur W. Thomas has accepted the appointment as head of the Department of Chemistry. Wortley F. Rudd, head of the School of Pharmacy of the Medical College of Virginia delivered the address to the graduates of the College of Pharmacy of Columbia University. He closed his address with the following words:

"You have entered to-night into fellowship with many of the world's elect. This new relationship demands much from you in return. You have made a start on the second-mile road. Will you keep on it? Will you, by loyalty, and tolerance, and fairness and kindliness and dependability and courage, make for yourselves a permanent place in this group which I believe always has and will in the future, save civilization if it is to be saved at all?"

AMERICAN MEDICAL ASSOCIATION.

The annual convention of the American Medical Association, held at Atlantic City, was the largest in its history; about 10,000 practicing physicians were present. "Socialized Medicine" was a topic of importance and will have further consideration during the coming year. The House of Delegates placed the Association at the service of the Federal Government. The exhibits attracted attention and the meeting indicated progress and development.

NEW JERSEY COLLEGE OF PHARMACY PRIZES.

At the annual senior-alumni dinner of the New Jersey College of Pharmacy held June 1st, in Newark, the New Jersey Pharmaceutical Association prizes were awarded to Ann O. Edison, wife of Theodore Edison, son of the late inventor, and to Fred Ninger of Wood Ridge. The chemistry and pharmacy prizes went to Julius Klugman of Newark.

PHARMACY—CHEMISTRY BUILDING U. OF WASHINGTON.

The Pharmacy—Chemistry Building of the University of Washington is under construction on the campus. Pharmacy will occupy a portion of the main floor and all of the third floor. Dean C. W. Johnson hopes to move in at the opening of school next fall.

THE NATIONAL ASSOCIATION OF BOARDS OF PHARMACY.

The annual convention of the National Association of Boards of Pharmacy will be held at the Hotel Pennsylvania, New York City, on August 16 and 17, 1937 (Monday and Tuesday). The convention of our parent body, the AMERICAN PHARMACEUTICAL ASSOCIATION, will commence on Wednesday and continue throughout the week. The Joint Session with the colleges will be held on Tuesday morning as usual, but

this year the AMERICAN PHARMACEUTICAL ASSOCIATION has been invited to participate.

H. G. Ruenzel, for thirty-six years member of the Wisconsin Board of Pharmacy, has retired. He was Secretary of the Board for twenty-five years.

Governor Lafollette has appointed **Edwin S. Schweger** of Green Bay to succeed Mr. Ruenzel. He is owner of two drug stores in Green Bay.

DELAWARE.

The annual convention of the Delaware Pharmaceutical Society (its fifty-first), was held June 28th–29th, at the Hotel Henlopen, Rehoboth Beach.

ARIZONA.

Druggists of Arizona joined in the Tri-State convention, held in El Paso, Texas, June 14th–17th. Arizona participated with pharmacists from the states of Texas and New Mexico in this meeting. A special train carried about 150 members of the Arizona association; many of these stayed over for the post-convention trip to Mexico City. W. U. Paul, of El Paso, was chairman of arrangements.

MEDICAL COLLEGE OF VIRGINIA.

Commencement exercises closing the ninety ninth session of the Medical College of Virginia was held at the Mosque Theatre, June 1st, at eight o'clock. Howard W. Blakeslee, Science Editor, the Associated Press, was the speaker. The honorary degree of Doctor of Science was conferred upon Dr. Irl C. Riggin, State Health Commissioner, Richmond, Virginia. This year there were twenty graduates in pharmacy.

OREGON AND MONTANA IN JULY.

The Oregon and Montana associations have selected July for their meetings and the same days in that month—July 12th–14th. Oregon will meet at the Seaside Hotel, Seaside, while Montana's headquarters will be at the Finlen Hotel, Butte.

MISSISSIPPI.

Mississippi State Pharmaceutical Association entertained with what is said to have been its biggest and best convention, from June 14th to June 16th. The convention headquarters were in the Buena Vista Hotel, which is located on the beach at Biloxi, on the historic and romantic Old Spanish Trail.

NORTH CAROLINA.

Nominations for 1938–1939 officers, who will be elected by mail ballot within the next few months and take office at Asheville, were made as follows: C. C. Fordham, Jr., of Greensboro and D. L. Boone of Durham, *President;* Phil D. Gattis of Raleigh and D. D. Hocutt of Henderson, *First Vice-President;* Joe Hollingsworth of Mount Airy and R. E. Kibler of Morganton, *Second Vice-President;* Carl Durham of Chapel Hill and I. T. Reamer of Durham, *Third Vice-President;* J. G. Beard and J. T. Holshouser, both of Chapel Hill, *Secretary-Treasurer.*

New officers, elected by mail ballot last year, were installed at the final business meeting Wednesday. They are: P. J. Suttlemyre of Hickory, *President;* C. C. Fordham, Jr., of Greensboro, J. C. Brantley, Jr., of Raleigh and Joseph Hollingsworth of Mount Airy, *Vice-Presidents;* Dean J. G. Beard of Chapel Hill, Secretary-Treasurer. E. E. Thomas of Roxboro, R. A. McDuffie of Greensboro and retiring President W. C. Ferrell of Nashville were installed as *Members of the Executive Committee.*

SOUTH CAROLINA.

"Victory Celebration" was held in Charleston, the city of romance with a wealth of old world charm in its beautiful gardens, unusual architecture. This was the 61st annual meeting and designated a never-to-be-forgotten convention.

ALABAMA.

"Reorganization" was the theme of the 55th annual convention of the Alabama Pharmaceutical Association, held in Montgomery, the capital city, June 16th–18th. President Sam J. Watkins believes that the time has come when every Congressional District in the State of Alabama must be organized in the interests of the retail drug industry.

WEST VIRGINIA.

West Virginia held a most interesting convention at Clarksburg, June 14th–15th. Among the speakers and visitors were: President George D. Beal of the AMERICAN PHARMACEUTICAL ASSOCIATION, former president R. L. Swain, Ralph W. Clark. The State Board of Pharmacy sessions were held in Morgantown, June 10th–12th.

LEGAL AND LEGISLATIVE.

FOOD AND DRUG BILL ACTION PROMISED SOON.

The House Committee on interstate and foreign commerce has taken no action as yet on the related food and drug and Federal Trade Commission bills pending before it, although members of the committee state that the subject will be reached soon. Meanwhile, Representative Thomas A. Jenkins of Ohio has introduced a bill (H. R. 7262) to expand the powers of the Federal Trade Commission generally and to give it specific jurisdiction over food and drug advertising.

AMENDMENT TO REGULATIONS GOVERNING THE KEEPING OF RECORDS OF DISPOSITIONS OF EXEMPT PREPARATIONS.

Pursuant to the authority contained in Section 6 of the Act of December 17, 1914 (38 Stat. 785, 789; U. S. Code (1934 Ed.) Title 26, Sec. 1041), as amended by Section 1007 of the Revenue Act of 1918 (40 Stat. 1057, 1132; U. S. Code (1934 Ed.), Title 26, Sec. 1041), Article 107 of Narcotic Regulations No. 5 is hereby amended to read as follows:

ARTICLE 107.

Records.—Every manufacturer, producer, compounder or vendor (including dispensing physicians), of exempt preparations must keep a record of all sales, exchanges, gifts or other dispositions, the entries to be made at the time of delivery. This record must show the name, address and registry number of the dealer to whom the preparation or remedy is sold, exchanged or given, the name and quantity of the preparation or remedy, and the date upon which delivery to the purchaser or his agent or the carrier is made. A separate record must also be kept of disposals to persons other than dealers, showing the name of the person to whom the preparation or remedy is sold, exchanged or given, made at the time of delivery, his address, the name and quantity of the preparation or remedy, and the date of delivery. The requirement of keeping a record of sales, exchanges or gifts to persons other than dealers will be deemed to be complied with, if made pursuant to prescriptions, issued by registered physicians, calling for exempt narcotic preparations or remedies, if the information called for in the preceding sentence is shown on the prescription, and the prescription is kept on the narcotic prescription file.

The Government does not furnish blanks for the keeping of these records.

The form of blanks for record by retailers must contain the date of sale, name of purchaser and address; the name of preparation and quantity. Forms are given on T. D. 26.

NARCOTIC SALES.

The *Pacific Drug Review* reports on a drug store, owned by a white man, catering entirely to negro trade, which fills from thirty to forty narcotic prescriptions per day and makes enough profit on these to pay all store overhead, including a good salary for the proprietor. No other prescription stock is carried. Prescriptions are all for half-grain morphine tablets which the druggist buys in 5000 lots, keeps put up in screw-cap vials of a dozen each which he sells on prescription at 75 cents. One customer, a street beggar, is said to get two prescriptions filled every day for two dozen half-grain morphine tablets for which he pays $3.00 with an extra $2.00 for the doctor for writing the two prescriptions. Is it possible for such traffic to be carried on for any length of time?

George H. Miller, of Cleveland, O., was elected President of the Proprietary Association to succeed the late Frank A. Blair. The 55th annual convention of the Association was held in Cleveland during the week of May 29th.

ALCOHOL REGULATIONS IN BRIEF.

(The full discussion of regulations should be read and preserved.)

Druggists not having a Medicinal Spirits Stamp Tax:

May purchase alcohol or any spirituous liquor.

May use them in compounding prescriptions or in the preparation of medicines or toiletries, provided the finished products contain at least a medicinal dose of drugs to the ounce.

May make U. S. P. and N. F. Preparations classed as beverages, but these are subject to the same rules regarding use as are liquors.

May *not* supply alcohol or liquors to anyone (including physicians and dentists) in unchanged form. Must be unsuited for beverage use.

May *not* fill prescriptions for uncombined liquors.

May *not* sell the specified official preparations uncombined.

Must keep alcohol and liquors in original stamped packages, except withdrawals for immediate use.

Must *not* keep alcohol in unstamped shelf bottles.

May *not* manufacture or sell Tincture of Ginger.

Druggists having a Medicinal Spirits Stamp Tax:

May sell alcohol and liquors on prescription and over the counter at retail (subject to state and local laws) in quantities of less than five gallons; and use in compounding.

May *not* manufacture Tincture of Ginger (liable as a rectifier) but may sell at retail.

General Precautions: See that strip stamps are in place on all unopened packages of alcohol or liquor; that a part of the stamp remains on package when opened and in use; destroy all stamps immediately upon emptying. Break all liquor bottles immediately upon emptying.—From *N. A. R. D. Journal*, June 3, 1937.

TEXAS BARBITURIC ACID LAW REPEALED.

The Texas legislature, by almost an unanimous vote in both houses, recently repealed the so-called Barbituric Acid Law. A former legislature passed a law placing certain restrictions on the sale of barbituric acid derivatives. The law requires that the druggists make their orders for the drug in triplicate, one copy to be sent to the State Health Department at Austin, one copy to the concern from whom the drug was purchased and one copy to be filed by the druggist. The law was practically impossible of enforcement.

Texas House Bill 1024, requiring manufacturers to replace drug products over two years old. The bill has been favorably reported with an amendment.

Tennessee Senate Bill 440 (House Bill 641). A tax of $200.00 a year on each vitamin claimed in the labeling or advertising of a preparation.

The Advisory Committee to the Public Health Service has presented recommendations for a Venereal Disease Control Program in state and local health departments published in reprint No. 54, and may be had from the Government Printing Office.

Charles R. Walgreen has donated $550,000.00 to the University of Chicago for the establishment of an institute to study American principles. This gift will be augmented by a donation of $275,000.00 from the Rosenwald fund. The institute will establish research in the principles and background of American institutions.

BOOK NOTICES AND REVIEWS.

Medicinal Plants of France. The Center of Technical and Economic Documentation on Medicinal and Aromatic Plants (formerly the National office of Primary Vegetable Substances for the Perfumery and Drug Industries), continuing the work already undertaken, has just published a new series of plates in color of wild and cultivated medicinal plants. This is the 4th series of the 3rd Volume. The first two volumes, containing two articles and 104 plates, represent the complete collection up-to-date. A few isolated series are exhausted and cannot be published again.

This 16th Series will be just as highly appreciated as the previous ones by everybody interested in Botany and Materia Medica. It will render the same service to collectors and cultivators of aromatic and medicinal plants and to educational courses of various kinds.

The 8 plates which make up this 16th Series represent: Medicinal and Industrial Algæ: Herb-Robert, Winter-Cherry, Wild Cherry Tree and Quince Tree, Rutaceæ, Genipi and Southernwood, Bedstraws, Perforated John's-Wort, officinal, and Carthusian Money-Wort.

The first 12 Series, published, can only be furnished now in two bound volumes (the second volume contains also 8 exotic species which are not cultivated in France) at the price of *60 francs for France* and *75 francs for foreign countries* for each volume. *Postage Additional.* Each volume carries an article by Professor Perrot. Address: C. D. P. M., 17, Rue Duguay-Trouin, Paris-6, France.

The AMERICAN PHARMACEUTICAL ASSOCIATION has been favored with a presentation copy of the Annual Report for 1936 by the Egyptian Government of the Central Narcotics Intelligence Bureau. The report was presented with the Directors' compliments, Lewa C. W. Russell Pasha, Commandant Cairo City Police. The volume of nearly 200 pages may be purchased at P. T. 10 from the Government Press, Bulaq, Cairo. The publication contains interesting data on all phases of narcotics, is illustrated by narcotic plants, means used by smugglers of narcotics, etc. Assays of narcotics are given and cultivation of plants are shown.

GENERAL PROGRAM FOR THE EIGHTY-FIFTH ANNUAL MEETING OF THE AMERICAN PHARMACEUTICAL ASSOCIATION AND RELATED ORGANIZATIONS, HOTEL PENNSYLVANIA, NEW YORK, N. Y., AUGUST 16–21, 1937.

AUGUST 10TH–13TH.

Plant Science Seminar. For the program see the A. PH. A. JOURNAL for June.

SATURDAY, AUGUST 14TH.

2:00 P.M. National Conference Pharmaceutical Research.
8:00 P.M. National Conference Pharmaceutical Research.

SUNDAY, AUGUST 15TH.

9:00 A.M. Council, A. PH. A.
8:00 P.M. American Council on Pharmaceutical Education.

MONDAY, AUGUST 16TH.

9:00 A.M. N. A. B. P.
9:00 A.M. A. A. C. P.—
Executive Committee.
Chemistry Conference.
Pharmacy Conference.
Pharmacognosy and Pharmacology Conference.
Pharmaceutical Economics Conference.
2:00 P.M. N. A. B. P.
2:00 P.M. A. A. C. P.
6:00 P.M. Dinner, N. A. B. P.
6:00 P.M. Dinner, A. A. C. P.
8:30 P.M. First Session, Conference Pharmaceutical Law Enforcement Officials.

TUESDAY, AUGUST 17TH.

9:00 A.M. Joint Conference, A. PH. A., N. A. B. P. and A. A. C. P.
12:15 P.M. Luncheon, Committee on National Formulary.
2:00 P.M. N. A. B. P.
2:00 P.M. A. A. C. P.
6:00 P.M. Dinner, Rho Chi Fraternity followed by Annual Meeting.
8:00 P.M. First General Session, A. PH. A.
10:30 P.M. President's Reception followed by Dancing.

WEDNESDAY, AUGUST 18TH.

9:00 A.M. First Session, House of Delegates.
12:15 P.M. Luncheon, Committee on Syllabus.
12:15 P.M. Luncheon, Kappa Psi Fraternity and Lambda Kappa Sigma Sorority.
12:15 P.M. Luncheon, Phi Delta Chi Fraternity.
2:00 P.M. Council, A. PH. A.
2:00 P.M. First Session, Scientific Section.
2:00 P.M. First Session, Section on Education and Legislation.
2:00 P.M. First Session, Section on Practical Pharmacy and Dispensing.
2:00 P.M. First Session, Section on Historical Pharmacy.
2:00 P.M. First Session, Section on Commercial Interests.
2:00 P.M. First Session, Conference Pharmaceutical Association Secretaries.
3:00 P.M. Meeting, Committee on Nominations.
3:00 P.M. Meeting, Committee on Resolutions.
7:00 P.M. Joint Banquet, A. PH. A. and Related Organizations.

THURSDAY, AUGUST 19TH.

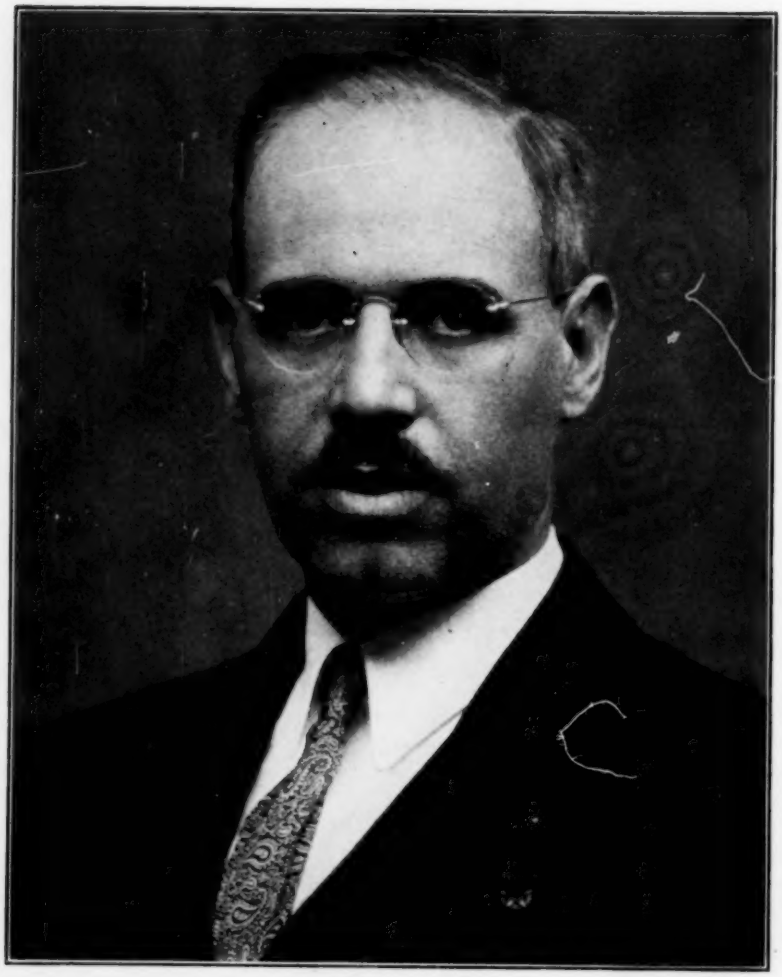
9:00 A.M. Second General Session, A. PH. A.
12:00 M. Veteran Druggists' Luncheon.
2:00 P.M. Boat Ride up the Hudson River.
6:00 P.M. Dinner at Bear Mountain Inn.
8:00 P.M. Return Boat Ride to New York.
8:15 P.M. Second Session, House of Delegates (to be held on the boat).

FRIDAY, AUGUST 20TH.

9:00 A.M. Joint Session, Scientific Section and Section on Practical Pharmacy and Dispensing.
9:00 A.M. Session, Sub-Section on Hospital Pharmacy.
9:00 A.M. Joint Session, Section on Education and Legislation, Conference Law Enforcement Officials and Conference of Pharmaceutical Association Secretaries.
12:15 P.M. Special Luncheons.
2:00 P.M. Second Session, Scientific Section.
2:00 P.M. Second Session, Section on Education and Legislation.
2:00 P.M. Second Session, Section on Practical Pharmacy and Dispensing.
2:00 P.M. Second Session, Section on Historical Pharmacy.
2:00 P.M. Second Session, Section on Commercial Interests.
2:00 P.M. Second Session, Conference Law Enforcement Officials.
2:00 P.M. Second Session, Conference Pharmaceutical Association Secretaries.
6:00 P.M. Dinner, Former Presidents, A. PH. A.
7:30 P.M. Meeting, Committee on Resolutions.
8:00 P.M. Final Session, House of Delegates.
10:00 P.M. Farewell Party and Dancing.

SATURDAY, AUGUST 21ST.

9:00 A.M. Final General Session, A. PH. A.
1:00 P.M. Council, A. PH. A.



JAMES C. MUNCH.